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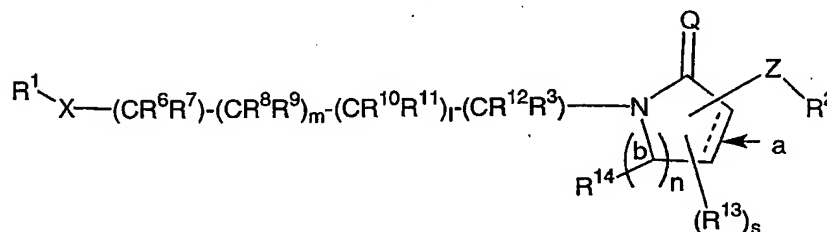
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[Continued on next page]

(54) Title: LACTAMS AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(I)

(57) Abstract: The present application describes modulators of MCP-1 of formula (I): or pharmaceutically acceptable salt forms thereof, useful for the prevention of asthma, multiple sclerosis, atherosclerosis, and rheumatoid arthritis.

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TITLE

LACTAMS AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

FIELD OF THE INVENTION

5 This invention relates generally to modulators of chemokine receptor activity, pharmaceutical compositions containing the same, and methods of using the same as agents for treatment and prevention of inflammatory diseases, allergic and autoimmune diseases,
10 and in particular, asthma, rheumatoid arthritis, atherosclerosis, and multiple sclerosis.

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines, of molecular
15 weight 6-15 kDa, that are released by a wide variety of cells to attract and activate, among other cell types, macrophages, T and B lymphocytes, eosinophils, basophils and neutrophils (reviewed in: Luster, *New Eng. J. Med.* 1998, 338, 436-445 and Rollins, *Blood* 1997, 90, 909-928).
20 There are two major classes of chemokines, CXC and CC, depending on whether the first two cysteines in the amino acid sequence are separated by a single amino acid (CXC) or are adjacent (CC). The CXC chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2
25 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils and T lymphocytes, whereas the CC chemokines, such as RANTES, MIP-1 α , MIP-1 β , the monocyte chemotactic proteins (MCP-1, MCP-2, MCP-3, MCP-4, and MCP-5) and the eotaxins (-1 and
30 -2) are chemotactic for, among other cell types, macrophages, T lymphocytes, eosinophils, dendritic cells, and basophils. There also exist the chemokines lymphotactin-1, lymphotactin-2 (both C chemokines), and

fractalkine (a CX₃C chemokine) that do not fall into either of the major chemokine subfamilies.

The chemokines bind to specific cell-surface receptors belonging to the family of G-protein-coupled
5 seven-transmembrane-domain proteins (reviewed in: Horuk, *Trends Pharm. Sci.* 1994, 15, 159-165) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal
10 though the associated trimeric G proteins, resulting in, among other responses, a rapid increase in intracellular calcium concentration, changes in cell shape, increased expression of cellular adhesion molecules, degranulation, and promotion of cell migration. There are at least ten human chemokine receptors that bind or respond to CC
15 chemokines with the following characteristic patterns (reviewed in Zlotnik and Oshie *Immunity* 2000, 12, 121): CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1 α , MCP-3, MCP-4, RANTES] (Ben-Barruch, et al., *Cell* 1993, 72, 415-425, and Luster, *New Eng. J. Med.* 1998, 338, 436-
20 445); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2B" or "CC-CKR-2A"/"CC-CKR-2B") [MCP-1, MCP-2, MCP-3, MCP-4, MCP-5] (Charo, et al., *Proc. Natl. Acad. Sci. USA* 1994, 91, 2752-2756, and Luster, *New Eng. J. Med.* 1998, 338, 436-445); CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin-1,
25 eotaxin-2, RANTES, MCP-3, MCP-4] (Combadiere, et al., *J. Biol. Chem.* 1995, 270, 16491-16494, and Luster, *New Eng. J. Med.* 1998, 338, 436-445); CCR-4 (or "CKR-4" or "CC-CKR-4") [TARC, MDC] (Power, et al., *J. Biol. Chem.* 1995, 270, 19495-19500, and Luster, *New Eng. J. Med.* 1998, 338,
30 436-445); CCR-5 (or "CKR-5" OR "CC-CKR-5") [MIP-1 α , RANTES, MIP-1 β] (Sanson, et al., *Biochemistry* 1996, 35, 3362-3367); CCR-6 (or "CKR-6" or "CC-CKR-6") [LARC]

(Baba, et al., *J. Biol. Chem.* 1997, 272, 14893-14898); CCR-7 (or "CKR-7" or "CC-CKR-7") [ELC] (Yoshie et al., *J. Leukoc. Biol.* 1997, 62, 634-644); CCR-8 (or "CKR-8" or "CC-CKR-8") [I-309] (Napolitano et al., *J. Immunol.*, 5 1996, 157, 2759-2763); CCR-10 (or "CKR-10" or "CC-CKR-10") [MCP-1, MCP-3] (Bonini, et al., *DNA and Cell Biol.* 1997, 16, 1249-1256); and CCR-11 [MCP-1, MCP-2, and MCP-4] (Schweickert, et al., *J. Biol. Chem.* 2000, 275, 90550).

10 In addition to the mammalian chemokine receptors, mammalian cytomegaloviruses, herpesviruses and poxviruses have been shown to express, in infected cells, proteins with the binding properties of chemokine receptors (reviewed in: Wells and Schwartz, *Curr. Opin. Biotech.* 15 1997, 8, 741-748). Human CC chemokines, such as RANTES and MCP-3, can cause rapid mobilization of calcium via these virally encoded receptors. Receptor expression may be permissive for infection by allowing for the subversion of normal immune system surveillance and 20 response to infection. Additionally, human chemokine receptors, such as CXCR4, CCR2, CCR3, CCR5 and CCR8, can act as co-receptors for the infection of mammalian cells by microbes as with, for example, the human immunodeficiency viruses (HIV).

25 The chemokines and their cognate receptors have been implicated as being important mediators of inflammatory, infectious, and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and 30 atherosclerosis (reviewed in: P. H. Carter, *Current Opinion in Chemical Biology* 2002, 6, 510; Trivedi, et al, *Ann. Reports Med. Chem.* 2000, 35, 191; Saunders and Tarby, *Drug Disc. Today* 1999, 4, 80; Premack and Schall,

Nature Medicine 1996, 2, 1174). For example, the chemokine monocyte chemoattractant-1 (MCP-1) and its receptor CC Chemokine Receptor 2 (CCR-2) play a pivotal role in attracting leukocytes to sites of inflammation and in subsequently activating these cells. When the chemokine MCP-1 binds to CCR-2, it induces a rapid increase in intracellular calcium concentration, increased expression of cellular adhesion molecules, cellular degranulation, and the promotion of leukocyte migration. Demonstration of the importance of the MCP-1/CCR-2 interaction has been provided by experiments with genetically modified mice. MCP-1 $-/-$ mice had normal numbers of leukocytes and macrophages, but were unable to recruit monocytes into sites of inflammation after several different types of immune challenge (Bao Lu, et al., *J. Exp. Med.* 1998, 187, 601). Likewise, CCR-2 $-/-$ mice were unable to recruit monocytes or produce interferon- γ when challenged with various exogenous agents; moreover, the leukocytes of CCR-2 null mice did not migrate in response to MCP-1 (Landin Boring, et al., *J. Clin. Invest.* 1997, 100, 2552), thereby demonstrating the specificity of the MCP-1/CCR-2 interaction. Two other groups have independently reported equivalent results with different strains of CCR-2 $-/-$ mice (William A. Kuziel, et al., *Proc. Natl. Acad. Sci. USA* 1997, 94, 12053, and Takao Kurihara, et al., *J. Exp. Med.* 1997, 186, 1757). The viability and generally normal health of the MCP-1 $-/-$ and CCR-2 $-/-$ animals is noteworthy, in that disruption of the MCP-1/CCR-2 interaction does not induce physiological crisis. Taken together, these data lead one to the conclusion that molecules that block the actions of MCP-1 would be useful in treating a number of inflammatory and autoimmune disorders. This hypothesis

has now been validated in a number of different animal disease models, as described below.

It is known that MCP-1 is upregulated in patients with rheumatoid arthritis (Alisa Koch, et al., *J. Clin. Invest.* 1992, 90, 772 - 779). Moreover, several studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating rheumatoid arthritis. A DNA vaccine encoding MCP-1 was shown recently to ameliorate chronic polyadjuvant-induced arthritis in rats (Sawsan Youssef, et al., *J. Clin. Invest.* 2000, 106, 361). Likewise, inflammatory disease symptoms could be controlled via direct administration of antibodies for MCP-1 to rats with collagen-induced arthritis (Hiroomi Ogata, et al., *J. Pathol.* 1997, 182, 106), or streptococcal cell wall-induced arthritis (Ralph C. Schimmer, et al., *J. Immunol.* 1998, 160, 1466). Perhaps most significantly, a peptide antagonist of MCP-1, MCP-1(9-76), was shown both to prevent disease onset and to reduce disease symptoms (depending on the time of administration) in the MRL-lpr mouse model of arthritis (Jiang-Hong Gong, et al., *J. Exp. Med.* 1997, 186, 131).

It is known that MCP-1 is upregulated in atherosclerotic lesions, and it has been shown that circulating levels of MCP-1 are reduced through treatment with therapeutic agents, plays a role in disease progression (Abdolreza Rezaie-Majd, et al, *Arterioscler. Thromb. Vasc. Biol.* 2002, 22, 1194 - 1199). Four key studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating atherosclerosis. For example, when MCP-1 $-/-$ mice are mated with LDL receptor-deficient mice, an 83% reduction in aortic lipid deposition was observed (Long Gu, et al., *Mol. Cell* 1998, 2, 275). Similarly, when MCP-1 was

genetically ablated from mice which already overexpressed human apolipoprotein B, the resulting mice were protected from atherosclerotic lesion formation relative to the MCP-1 +/+ apoB control mice (Jennifa Gosling, et al., *J. Clin. Invest.* 1999, 103, 773). Likewise, when CCR-2 -/- mice are crossed with apolipoprotein E -/- mice, a significant decrease in the incidence of atherosclerotic lesions was observed (Landin Boring, et al, *Nature* 1998, 394, 894). Finally, when apolipoprotein E -/- mice are administered a gene encoding a peptide antagonist of CCR2, then lesion size is decreased and plaque stability is increased (W. Ni, et al. *Circulation* 2001, 103, 2096 - 2101).

It is known that MCP-1 is upregulated in human multiple sclerosis, and it has been shown that effective therapy with interferon b-1b reduces MCP-1 expression in peripheral blood mononuclear cells, suggesting that MCP-1 plays a role in disease progression (Carla Iarlori, et al., *J. Neuroimmunol.* 2002, 123, 170 - 179). Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR-2 interaction in treating multiple sclerosis; all of these studies have been demonstrated in experimental autoimmune encephalomyelitis (EAE), the conventional animal model for multiple sclerosis. Administration of antibodies for MCP-1 to animals with EAE significantly diminished disease relapse (K. J. Kennedy, et al., *J. Neuroimmunol.* 1998, 92, 98). Furthermore, two recent reports have now shown that CCR-2 -/- mice are resistant to EAE (Brian T. Fife, et al., *J. Exp. Med.* 2000, 192, 899; Leonid Izikson, et al., *J. Exp. Med.* 2000, 192, 1075).

It is known that MCP-1 is upregulated in patients who develop bronchiolitis obliterans syndrome after lung

transplantation (Martine Reynaud-Gaubert, et al., *J. of Heart and Lung Transplant.*, 2002, 21, 721 - 730; John Belperio, et al., *J. Clin. Invest.* 2001, 108, 547 - 556). In a murine model of bronchiolitis obliterans syndrome, 5 administration of an antibody to MCP-1 led to attenuation of airway obliteration; likewise, CCR2 -/- mice were resistant to airway obliteration in this same model (John Belperio, et al., *J. Clin. Invest.* 2001, 108, 547 - 556). These data suggest that antagonism of MCP-1/CCR2 may be 10 beneficial in treating rejection of organs following transplantation.

Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating asthma. Sequestration of MCP-1 15 with a neutralizing antibody in ovalbumin-challenged mice resulted in marked decrease in bronchial hyperresponsiveness and inflammation (Jose-Angel Gonzalo, et al., *J. Exp. Med.* 1998, 188, 157). It proved possible to reduce allergic airway inflammation in *Schistosoma* 20 *mansoni* egg-challenged mice through the administration of antibodies for MCP-1 (Nicholas W. Lukacs, et al., *J. Immunol.* 1997, 158, 4398). Consistent with this, MCP-1 -/- mice displayed a reduced response to challenge with *Schistosoma mansoni* egg (Bao Lu, et al., *J. Exp. Med.* 25 1998, 187, 601).

Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating kidney disease. Administration of antibodies for MCP-1 in a murine model of 30 glomerulonephritis resulted in a marked decrease in glomerular crescent formation and deposition of type I collagen (Clare M. Lloyd, et al., *J. Exp. Med.* 1997, 185, 1371). In addition, MCP-1 -/- mice with induced

nephrotoxic serum nephritis showed significantly less tubular damage than their MCP-1 $+/+$ counterparts (Gregory H. Tesch, et al., *J. Clin. Invest.* 1999, 103, 73).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating systemic lupus erythematosus. Crossing of MCP-1 $-/-$ mice with MRL-*FAS^{lpr}* mice -- the latter of which have a fatal autoimmune disease that is analogous to human systemic lupus erythematosus -- results mice that have less disease and longer survival than the wildtype MRL-*FAS^{lpr}* mice (Gregory H. Tesch, et al., *J. Exp. Med.* 1999, 190, 1813).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating colitis. CCR-2 $-/-$ mice were protected from the effects of dextran sodium sulfate-induced colitis (Pietro G. Andres, et al., *J. Immunol.* 2000, 164, 6303).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating alveolitis. When rats with IgA immune complex lung injury were treated intravenously with antibodies raised against rat MCP-1 (JE), the symptoms of alveolitis were partially alleviated (Michael L. Jones, et al., *J. Immunol.* 1992, 149, 2147).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating cancer. When immunodeficient mice bearing human breast carcinoma cells were treated with an anti-MCP-1 antibody, inhibition of lung micrometastases and increases in survival were observed (Rosalba Salcedo, et al., *Blood* 2000, 96, 34 - 40).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in

treating restinosis. Mice deficient in CCR2 showed reductions in the intimal area and in the intima/media ratio (relative to wildtype littermates) after injury of the femoral artery (Merce Roque, et al. *Arterioscler.*

5 *Thromb. Vasc. Biol.* 2002, 22, 554 - 559).

Other studies have provided evidence that MCP-1 is overexpressed in various disease states not mentioned above. These reports provide correlative evidence that MCP-1 antagonists could be useful therapeutics for such

10 diseases. Two reports described the overexpression of MCP-1 in the intestinal epithelial cells and bowel mucosa of patients with inflammatory bowel disease (H. C. Reinecker, et al., *Gastroenterology* 1995, 108, 40, and Michael C. Grimm, et al., *J. Leukoc. Biol.* 1996, 59,

15 804). Two reports describe the overexpression of MCP-1 rats with induced brain trauma (J. S. King, et al., *J. Neuroimmunol.* 1994, 56, 127, and Joan W. Berman, et al., *J. Immunol.* 1996, 156, 3017). Another study has demonstrated the overexpression of MCP-1 in rodent

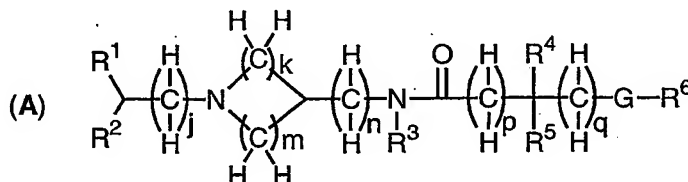
20 cardiac allografts, suggesting a role for MCP-1 in the pathogenesis of transplant arteriosclerosis (Mary E. Russell, et al. *Proc. Natl. Acad. Sci. USA* 1993, 90, 6086). The overexpression of MCP-1 has been noted in the lung endothelial cells of patients with idiopathic

25 pulmonary fibrosis (Harry N. Antoniades, et al., *Proc. Natl. Acad. Sci. USA* 1992, 89, 5371). Similarly, the overexpression of MCP-1 has been noted in the skin from patients with psoriasis (M. Deleuran, et al., *J. Dermatol. Sci.* 1996, 13, 228, and R. Gillitzer, et al.,

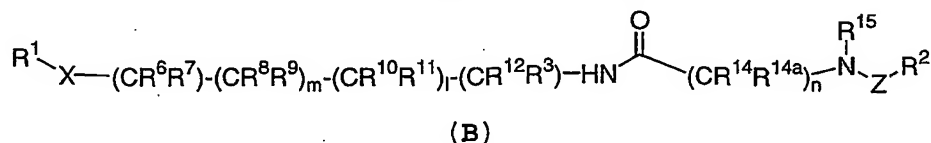
30 *J. Invest. Dermatol.* 1993, 101, 127). Finally, a recent report has shown that MCP-1 is overexpressed in the brains and cerebrospinal fluid of patients with HIV-1-associated dementia (Alfredo Garzino-Demo, WO 99/46991).

It should also be noted that CCR-2 has been implicated as a co-receptor for some strains of HIV (B. J. Doranz, et al., *Cell* 1996, 85, 1149). It has also been determined that the use of CCR-2 as an HIV co-receptor can be correlated with disease progression (Ruth I. Connor, et al., *J. Exp. Med.* 1997, 185, 621). This finding is consistent with the recent finding that the presence of a CCR-2 mutant, CCR2-64I, is positively correlated with delayed onset of HIV in the human population (Michael W. Smith, et al., *Science* 1997, 277, 959). Although MCP-1 has not been implicated in these processes, it may be that MCP-1 antagonists that act via binding to CCR-2 may have beneficial therapeutic effects in delaying the disease progression to AIDS in HIV-infected patients.

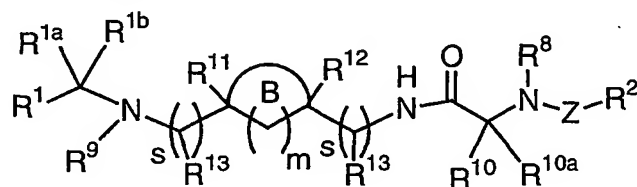
Recently, a number of groups have described the development of small molecule antagonists of MCP-1 (reviewed in: Bharat K. Trivedi, et al, *Ann. Reports Med. Chem.* 2000, 35, 191). Workers at Teijen and Combichem reported the use of cyclic amines (A) as MCP-1 (Tatsuki Shiota, et al., WO 99/25686; Tatsuki Shiota, et al., WO 00/69815) and MIP-1 α (Christine Tarby and Wilna Moree, WO 00/69820) antagonists.



Workers at Bristol-Myers Squibb have reported the use of acyclic diamines (B) as MCP-1 antagonists (Percy Carter and Robert Cherney, WO-02/50019).

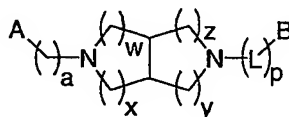


Workers at Bristol-Myers Squibb have reported the use of cyclic diamines (C) as MCP-1 antagonists (Robert Cherney, WO-02/060859).



(C)

Workers at Pfizer have reported the use of bicyclic diamines (D) as MCP-1 antagonists (Roberto Colon-Cruz, et al., WO-02/070523).



(D)

A number of other groups have also described the development of small molecule antagonists of the MCP-1/CCR-2 interaction. To date, indolopiperidines (Ian T. Forbes, et al., *Bioorg. Med. Chem. Lett.* 2000, 10, 1803), spiropiperidines (Tara Mirzadegan, et al., *J. Biol. Chem.* 2000, 275, 25562), quaternary amines (Masanori Baba, et al., *Proc. Natl. Acad. Sci.* 1999, 96, 5698), 2-substituted indoles (Alan Faull and Jason Kettle, WO 00/46196; Andrew John Barker, et al., WO 99/07351; Andrew John Barker, et al., WO 99/07678), pyrazolone derivatives (Janak Khimchand Padia, et al., US patent 6,011,052, 2000), 2-substituted benzimidazoles (David Thomas Connor, et al., WO 98/06703), N, N-dialkylhomopiperazines (T. Shiota, et al., WO 97/44329), bicyclic pyrroles (Andrew J. Barker, et al., WO 99/40913 and Andrew J. Barker, et al., WO 99/40914), and 5-aryl pentadienamides (K. G. Carson, et al., Cambridge Health Tech Institute Chemokine

Symposium, McLean, VA, USA, 1999) have all been reported as MCP-1 antagonists.

The foregoing reference compounds are readily distinguished structurally from the present invention by virtue of substantial differences in the terminal functionality, the attachment functionality, or the core functionality. The prior art does not disclose nor suggest the unique combination of structural fragments that embody in the novel compounds described herein. Furthermore, the prior art does not disclose or suggest that the compounds of the present invention would be antagonists of MCP-1.

It should be noted that CCR-2 is also the receptor for the chemokines MCP-2, MCP-3, MCP-4, and MCP-5 (Luster, *New Eng. J. Med.* 1998, 338, 436-445). Since the new compounds of formula (I) described herein antagonize MCP-1 by binding to the CCR-2 receptor, it may be that these compounds of formula (I) are also effective antagonists of the actions of MCP-2, MCP-3, MCP-4, and MCP-5 that are mediated by CCR-2. Accordingly, when reference is made herein to "antagonism of MCP-1," it is to be assumed that this is equivalent to "antagonism of chemokine stimulation of CCR-2."

SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel antagonists or partial agonists/antagonists of MCP-1 receptor activity, or pharmaceutically acceptable salts or prodrugs thereof.

The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

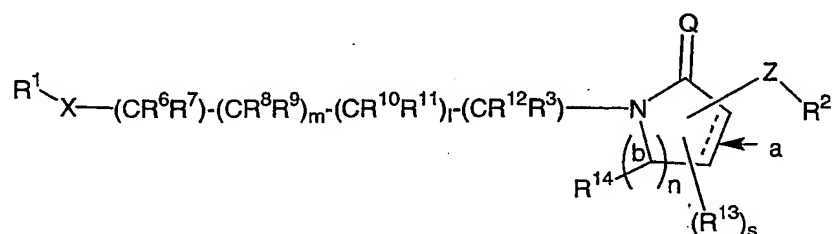
The present invention provides a method for treating rheumatoid arthritis, multiple sclerosis, and atherosclerosis, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides diamine compounds for use in therapy.

The present invention provides the use of novel diamine compounds for the manufacture of a medicament for the treatment of inflammatory diseases.

These and other features of the invention, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

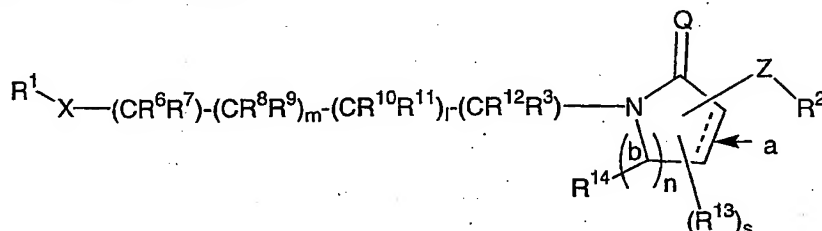


(I)

or stereoisomers or pharmaceutically acceptable salts thereof, wherein Q, X, Z, l, m, n, s, R¹, R², R³, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹⁴ and R¹⁴ᵃ are defined below, are effective modulators of chemokine activity.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides novel compounds of formula (I):



5

(I)

or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

- 10 Z is selected from a bond, -NR¹⁸C(O)-, -NR¹⁸C(S)-, -NR¹⁸C(O)NH-, -NR¹⁸C(S)NH-, -NR¹⁸SO₂-, -NR¹⁸SO₂NH-, -C(O)NR¹⁸-, -OC(O)NR¹⁸-, -NR¹⁸C(O)O-, -(CR²⁵R²⁵)ₜ-, -CR²⁴=CR²⁴-, -CR²⁵R²⁵C(O)-, -C(O)CR²⁵R²⁵-, CR²⁵R²⁵C(=N-OR²⁶)-, -O-CR²⁴R²⁴-, -C R²⁴R²⁴-O-, -O-,
- 15 -NR¹⁹-, -NR¹⁹-CR²⁴R²⁴-, -CHR²⁴-NR¹⁹-, -S(O)ₚ-, -S(O)ₚ-CR²⁴R²⁴-, and -S(O)ₚ-NR¹⁹-;

Q is selected from O or S;

- 20 wherein neither Z nor R¹³ are connected to a carbon atom labeled (b);

X is selected from -NR¹⁷- and -CHR¹⁶NR¹⁷-;

- 25 bond (a) is a single or double bond;

alternatively, when n is equal to 2, two atoms labeled (b) may join through a double bond;

- 30 R¹ is selected from a C₆-₁₀ aryl group substituted with 0-5 R⁴ and a 5-10 membered heteroaryl system

containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁴;

R² is selected from a C₆₋₁₀ aryl group substituted with
 5 0-5 R⁵ and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁵;

R³ is selected from H, (CRR)_qOH, (CRR)_qSH, (CRR)_qOR^{3d},
 10 (CRR)_qS(O)_pR^{3d}, (CRR)_rC(O)R^{3b}, (CRR)_qNR^{3a}R^{3a},
 (CRR)_rC(O)NR^{3a}R^{3a}, (CRR)_rC(O)NR^{3a}OR^{3d},
 (CRR)_qSO₂NR^{3a}R^{3a}, (CRR)_rC(O)OR^{3d}, a (CRR)_r-C₃₋₁₀
 carbocyclic residue substituted with 0-5 R^{3e}, and a
 15 (CRR)_r-5-10 membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-3 R^{3e};

with the proviso that R³ is not H if R⁶ is H;

20 alternatively, R³ and R¹² join to form a C₃₋₆ cycloalkyl substituted with 0-2 R^{3g}, a 5-6 membered lactam ring in which carbon atoms of the ring are substituted with 0-2 R^{3g}, or a 5-6 membered lactone ring in which carbon atoms of the ring are substituted with
 25 0-2 R^{3g};

R^{3a}, at each occurrence, is independently selected from H, methyl substituted with 0-1 R^{3c}, C₂₋₆ alkyl substituted with 0-3 R^{3e}, C₃₋₈ alkenyl substituted
 30 with 0-3 R^{3e}, C₃₋₈ alkynyl substituted with 0-3 R^{3e}, (CH₂)_rC₃₋₆ cycloalkyl, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{3e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4

heteroatoms selected from N, O, and S, substituted with 0-3 R^{3e};

R^{3b}, at each occurrence, is independently selected from
5 C₁₋₆ alkyl substituted with 0-3 R^{3e}, C₂₋₈ alkenyl substituted with 0-3 R^{3e}, C₂₋₈ alkynyl substituted with 0-3 R^{3e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{3e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms
10 selected from N, O, and S, substituted with 0-3 R^{3e};

R^{3c} is independently selected from -C(O)R^{3b}, -C(O)OR^{3d}, -C(O)NR^{3f}R^{3f}, and (CH₂)_rphenyl;

15 R^{3d}, at each occurrence, is independently selected from H, methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{3e}, C₃₋₆ alkenyl substituted with 0-3 R^{3e}, C₃₋₆ alkynyl substituted with 0-3 R^{3e}, a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{3e}, and a (CH₂)_r-5-6 membered
20 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3e};

R^{3e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
25 (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{3f}R^{3f}, and (CH₂)_rphenyl;

R^{3f}, at each occurrence, is selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

30

R^{3g} is selected from (CHR)_rOH, (CHR)_rSH, (CHR)_rOR^{3d},
 (CHR)_rS(O)_rR^{3d}, (CHR)_rC(O)R^{3b}, (CHR)_rNR^{3a}R^{3a},
 (CHR)_rC(O)NR^{3a}R^{3a}, (CHR)_rC(O)NR^{3a}OR^{3d},
 (CHR)_rSO₂NR^{3a}R^{3a}, (CHR)_rC(O)OR^{3d}, and a (CHR)_r-C₃₋₁₀
 5 carbocyclic residue substituted with 0-5 R^{3e};

R, at each occurrence, is independently selected from H,
 C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆
 cycloalkyl, (CHR)_rC(O)NR^{3a}R^{3a}, and (CHR)_rC(O)OR^{3d}, and
 10 (CH₂)_rphenyl substituted with 0-3 R^{3e}, and a
 (CH₂)_r-5-10 membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-3 R^{3e};

15 R⁴, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, Br,
 I, F, NO₂, CN, (CR'R')_rNR^{4a}R^{4a}, (CR'R')_rOH,
 (CR'R')_rO(CR'R')_rR^{4d}, (CR'R')_rSH, (CR'R')_rC(O)H,
 (CR'R')_rS(CR'R')_rR^{4d}, (CR'R')_rC(O)OH,
 20 (CR'R')_rC(O)(CR'R')_rR^{4b}, (CR'R')_rC(O)NR^{4a}R^{4a},
 (CR'R')_rNR^{4f}C(O)(CR'R')_rR^{4b}, (CR'R')_rC(O)O(CR'R')_rR^{4d},
 (CR'R')_rOC(O)(CR'R')_rR^{4b},
 (CR'R')_rNR^{4f}C(O)O(CR'R')_rR^{4d}, (CR'R')_rOC(O)NR^{4a}R^{4a},
 (CR'R')_rNR^{4a}C(S)NR^{4a}(CR'R')_rR^{4d},
 25 (CR'R')_rNR^{4a}C(O)NR^{4a}R^{4a}, (CR'R')_rC(=NR^{4f})NR^{4a}R^{4a},
 (CR'R')_rNHC(=NR^{4f})NR^{4f}R^{4f}, (CR'R')_rS(O)_p(CR'R')_rR^{4b},
 (CR'R')_rS(O)₂NR^{4a}R^{4a}, (CR'R')_rNR^{4f}S(O)₂NR^{4a}R^{4a},
 (CR'R')_rNR^{4f}S(O)₂(CR'R')_rR^{4b}, C₁₋₆ haloalkyl, C₂₋₈
 alkenyl substituted with 0-3 R', C₂₋₈ alkynyl
 30 substituted with 0-3 R', and (CR'R')_rphenyl
 substituted with 0-3 R^{4e};

alternatively, two R⁴ on adjacent atoms on R¹ may join to form a cyclic acetal;

5 R^{4a}, at each occurrence, is independently selected from H, methyl substituted with 0-1R^{4g}, C₂₋₆ alkyl substituted with 0-2 R^{4e}, C₃₋₈ alkenyl substituted with 0-2 R^{4e}, C₃₋₈ alkynyl substituted with 0-2 R^{4e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{4e}, and a (CH₂)_r-5-10 membered heterocyclic
10 system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e};

R^{4b}, at each occurrence, is selected from C₁₋₆ alkyl substituted with 0-2 R^{4e}, C₃₋₈ alkenyl substituted with 0-2 R^{4e}, C₃₋₈ alkynyl substituted with 0-2 R^{4e},
15 a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-3 R^{4e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e};

20 R^{4d}, at each occurrence, is selected from C₃₋₈ alkenyl substituted with 0-2 R^{4e}, C₃₋₈ alkynyl substituted with 0-2 R^{4e}, methyl, CF₃, C₂₋₆ alkyl substituted with 0-3 R^{4e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{4e}, and a (CH₂)_r-5-6 membered
25 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{4e};

30 R^{4e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_r-C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_r-CF₃, (CH₂)_r-OC₁₋₅ alkyl, OH, SH, (CH₂)_r-SC₁₋₅ alkyl, (CH₂)_r-NR^{4f}R^{4f}, and (CH₂)_r-phenyl;

R^{4f}, at each occurrence, is selected from H, C₁₋₅ alkyl, and C₃₋₆ cycloalkyl, and phenyl;

R^{4g} is independently selected from -C(O)R^{4b}, -C(O)OR^{4d},
 5 -C(O)NR^{4f}R^{4f}, and (CH₂)_rphenyl;

R⁵, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, Br, I, F, NO₂, CN, (CR'R')_rNR^{5a}R^{5a}, (CR'R')_rOH,
 10 (CR'R')_rO(CR'R')_rR^{5d}, (CR'R')_rSH, (CR'R')_rC(O)H, (CR'R')_rS(CR'R')_rR^{5d}, (CR'R')_rC(O)OH,
 (CR'R')_rC(O)(CR'R')_rR^{5b}, (CR'R')_rC(O)NR^{5a}R^{5a}, (CR'R')_rNR^{5f}C(O)(CR'R')_rR^{5b}, (CR'R')_rC(O)O(CR'R')_rR^{5d},
 (CR'R')_rOC(O)(CR'R')_rR^{5b}, (CR'R')_rNR^{5f}C(O)O(CR'R')_rR^{5d},
 15 (CR'R')_rOC(O)NR^{5a}R^{5a}, (CR'R')_rNR^{5a}C(O)NR^{5a}R^{5a}, (CR'R')_rC(=NR^{5f})NR^{5a}R^{5a}, (CR'R')_rNHC(=NR^{5f})NR^{5f}R^{5f},
 (CR'R')_rS(O)_p(CR'R')_rR^{5b}, (CR'R')_rS(O)₂NR^{5a}R^{5a}, (CR'R')_rNR^{5a}S(O)₂NR^{5a}R^{5a}, (CR'R')_rNR^{5f}S(O)₂(CR'R')_rR^{5b},
 C₁₋₆ haloalkyl, C₂₋₈ alkenyl substituted with 0-3 R',
 20 C₂₋₈ alkynyl substituted with 0-3 R', (CR'R')_rphenyl substituted with 0-3 R^{5e}, and a (CRR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5c};

25 alternatively, two R⁵ on adjacent atoms on R² may join to form a cyclic acetal;

R^{5a}, at each occurrence, is independently selected from H, methyl substituted with 0-1 R^{5g}, C₂₋₆ alkyl
 30 substituted with 0-2 R^{5e}, C₃₋₈ alkenyl substituted with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with

0-5 R^{5e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5e};

5 R^{5b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-2 R^{5e}, C₃₋₈ alkenyl substituted with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e}, a (CH₂)_rC₃₋₆ carbocyclic residue substituted with 0-3 R^{5e}, and a (CH₂)_r-5-6 membered
10 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5e};

R^{5d}, at each occurrence, is independently selected from C₃₋₈ alkenyl substituted with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e}, methyl, CF₃, C₂₋₆ alkyl substituted with 0-3 R^{5e}, a (CH₂)_r-C₃₋₁₀ carbocyclic
15 residue substituted with 0-3 R^{5e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{5e};
20

R^{5e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{5f}R^{5f}, and (CH₂)_rphenyl;
25

R^{5f}, at each occurrence, is selected from H, C₁₋₅ alkyl, and C₃₋₆ cycloalkyl, and phenyl;

30 R^{5g} is independently selected from -C(O)R^{5b}, -C(O)OR^{5d}, -C(O)NR^{5f}R^{5f}, and (CH₂)_rphenyl;

R', at each occurrence, is selected from H, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, and (CH₂)_rphenyl substituted with R^{5e};

5 R⁶, is selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, (CRR)_qOH, (CRR)_qSH, (CRR)_qOR^{6d}, (CRR)_qS(O)_pR^{6d}, (CRR)_rC(O)R^{6b}, (CRR)_rNR^{6a}R^{6a}, (CRR)_rC(O)NR^{6a}R^{6a}, (CRR)_rC(O)NR^{6a}OR^{6d}, (CRR)SO₂NR^{6a}R^{6a}, (CRR)_rC(O)OR^{6d}, a (CRR)_r-C₃₋₁₀ carbocyclic residue
 10 substituted with 0-5 R^{6e}, and a (CRR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e};

alternatively, R⁶ and R⁷ join to form a C₃₋₆ cycloalkyl
 15 substituted with 0-2 R^{6g}, a 5-6 membered ring lactam substituted with 0-2 R^{6g}, or a 5-6 membered ring lactone substituted with 0-2 R^{6g};

R^{6a}, at each occurrence, is independently selected from H,
 20 methyl, C₂₋₆ alkyl substituted with 0-3 R^{6e}, C₃₋₈ alkenyl substituted with 0-3 R^{6e}, C₃₋₈ alkynyl substituted with 0-3 R^{6e}, (CH₂)_rC₃₋₆ cycloalkyl, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{6e}, and a (CH₂)_r-5-10 membered heterocyclic system
 25 containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e};

R^{6b}, at each occurrence, is independently selected from
 C₁₋₆ alkyl substituted with 0-3 R^{6e}, C₂₋₈ alkenyl
 30 substituted with 0-3 R^{6e}, C₂₋₈ alkynyl substituted with 0-3 R^{6e}, a (CH₂)_r-C₃₋₆ carbocyclic residue

substituted with 0-2 R^{6e} , and a $(CH_2)_r$ -5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e} ;

5 R^{6d} , at each occurrence, is independently selected from H, methyl, $-CF_3$, C_{2-6} alkyl substituted with 0-3 R^{6e} , C_{3-6} alkenyl substituted with 0-3 R^{6e} , C_{3-6} alkynyl substituted with 0-3 R^{6e} , a C_{3-10} carbocyclic residue substituted with 0-3 R^{6e} , and a $(CH_2)_r$ -5-6 membered
 10 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e} ;

R^{6e} , at each occurrence, is independently selected from C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-6}
 15 cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, $-O-C_{1-6}$ alkyl, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{6f}R^{6f}$, and $(CH_2)_r$ phenyl;

R^{6f} , at each occurrence, is independently selected from H,
 20 C_{1-6} alkyl, and C_{3-6} cycloalkyl;

R^{6g} is selected from $(CHR)_qOH$, $(CHR)_qSH$, $(CHR)_qOR^{6d}$,
 $(CHR)_qS(O)_pR^{6d}$, $(CHR)_rC(O)R^{6b}$, $(CHR)_qNR^{6a}R^{6a}$,
 $(CHR)_rC(O)NR^{6a}R^{6a}$, $(CHR)_rC(O)NR^{6a}OR^{6d}$,
 25 $(CHR)_qSO_2NR^{6a}R^{6a}$, $(CHR)_rC(O)OR^{6d}$, and a $(CHR)_r$ - C_{3-10} carbocyclic residue substituted with 0-5 R^{6e} ;

R^7 , is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CRR)_qOH$, $(CRR)_qSH$, $(CRR)_qOR^{7d}$,
 30 $(CRR)_qS(O)_pR^{7d}$, $(CRR)_rC(O)R^{7b}$, $(CRR)_rNR^{7a}R^{7a}$,

(CRR)_rC(O)NR^{7a}R^{7a}, (CRR)_rC(O)NR^{7a}OR^{7d},
(CRR)_qSO₂NR^{7a}R^{7a}, (CRR)_rC(O)OR^{7d}, a (CRR)_r-C₃₋₁₀
carbocyclic residue substituted with 0-5 R^{7e}, and a
5 (CRR)_r-5-10 membered heterocyclic system containing
1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{7e};

R^{7a}, at each occurrence, is independently selected from H,
methyl, C₂₋₆ alkyl substituted with 0-3 R^{7e}, C₃₋₈
10 alkenyl substituted with 0-3 R^{7e}, C₃₋₈ alkynyl
substituted with 0-3 R^{7e}, (CH₂)_rC₃₋₆ cycloalkyl, a
(CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5
R^{7e}, and a (CH₂)_r-5-10 membered heterocyclic system
containing 1-4 heteroatoms selected from N, O, and
15 S, substituted with 0-3 R^{7e};

R^{7b}, at each occurrence, is independently selected from
C₁₋₆ alkyl substituted with 0-3 R^{7e}, C₂₋₈ alkenyl
substituted with 0-3 R^{7e}, C₂₋₈ alkynyl substituted
20 with 0-3 R^{7e}, a (CH₂)_r-C₃₋₆ carbocyclic residue
substituted with 0-2 R^{7e}, and a (CH₂)_r-5-6 membered
heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{7e};

25 R^{7d}, at each occurrence, is independently selected from H,
methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{7e},
C₃₋₆ alkenyl substituted with 0-3 R^{7e}, C₃₋₆ alkynyl
substituted with 0-3 R^{7e}, a C₃₋₁₀ carbocyclic residue
substituted with 0-3 R^{7e}, and a (CH₂)_r-5-6 membered

heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{7e};

R^{7e}, at each occurrence, is independently selected from
5 C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆
cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃,
(CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅
alkyl, (CH₂)_rNR^{7f}R^{7f}, and (CH₂)_rphenyl;

10 R^{7f}, at each occurrence, is independently selected from H,
C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

R⁸ is selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
alkynyl, (CRR)_rOH, (CRR)_rSH, (CRR)_rOR^{8d},
15 (CRR)_rS(O)_pR^{8d}, (CRR)_rC(O)R^{8b}, (CRR)_rNR^{8a}R^{8a},
(CRR)_rC(O)NR^{8a}R^{8a}, (CRR)_rC(O)NR^{8a}OR^{8d},
(CRR)_rSO₂NR^{8a}R^{8a}, (CRR)_rC(O)OR^{8d}, a (CRR)_r-C₃₋₁₀
carbocyclic residue substituted with 0-5 R^{8e}, and a
(CRR)_r-5-10 membered heterocyclic system containing
20 1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{8e};

alternatively, R⁸ and R⁹ join to form a C₃₋₆ cycloalkyl
substituted with 0-2 R^{8g}, a 5-6 membered ring lactam
25 substituted with 0-2 R^{8g}, or a 5-6 membered ring
lactone substituted with 0-2 R^{8g};

R^{8a}, at each occurrence, is independently selected from H,
methyl, C₂₋₆ alkyl substituted with 0-3 R^{8e}, C₃₋₈
30 alkenyl substituted with 0-3 R^{8e}, C₃₋₈ alkynyl
substituted with 0-3 R^{8e}, (CH₂)_rC₃₋₆ cycloalkyl, a

(CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{8e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{8e};

5

R^{8b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-3 R^{8e}, C₂₋₈ alkenyl substituted with 0-3 R^{8e}, C₂₋₈ alkynyl substituted with 0-3 R^{8e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{8e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{8e};

10

R^{8d}, at each occurrence, is independently selected from H, methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{8e}, C₃₋₆ alkenyl substituted with 0-3 R^{8e}, C₃₋₆ alkynyl substituted with 0-3 R^{8e}, a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{8e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{8e};

15

20

R^{8e}, at each occurrence, is independently selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{8f}R^{8f}, and (CH₂)_rphenyl;

25

R^{8f}, at each occurrence, is independently selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

30

R^{8g} is selected from (CHR)_qOH, (CHR)_qSH, (CHR)_qOR^{8d},
 (CHR)_qS(O)_pR^{8d}, (CHR)_rC(O)R^{8b}, (CHR)_qNR^{8a}R^{8a},
 (CHR)_rC(O)NR^{8a}R^{8a}, (CHR)_rC(O)NR^{8a}OR^{8d},
 (CHR)_qSO₂NR^{8a}R^{8a}, (CHR)_rC(O)OR^{8d}, and a (CHR)_r-C₃₋₁₀
 5 carbocyclic residue substituted with 0-5 R^{8e};

R⁹ is selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
 alkynyl, (CRR)_rOH, (CRR)_rSH, (CRR)_rOR^{9d},
 (CRR)_rS(O)_pR^{9d}, (CRR)_rC(O)R^{9b}, (CRR)_rNR^{9a}R^{9a},
 10 (CRR)_rC(O)NR^{9a}R^{9a}, (CRR)_rC(O)NR^{9a}OR^{9d},
 (CRR)_rSO₂NR^{9a}R^{9a}, (CRR)_rC(O)OR^{9d}, a (CRR)_r-C₃₋₁₀
 carbocyclic residue substituted with 0-5 R^{9e}, and a
 (CRR)_r-5-10 membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 15 substituted with 0-3 R^{9e};

R^{9a}, at each occurrence, is independently selected from H,
 methyl, C₂₋₆ alkyl substituted with 0-3 R^{9e}, C₃₋₈
 alkenyl substituted with 0-3 R^{9e}, C₃₋₈ alkynyl
 20 substituted with 0-3 R^{9e}, (CH₂)_rC₃₋₆ cycloalkyl, a
 (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5
 R^{9e}, and a (CH₂)_r-5-10 membered heterocyclic system
 containing 1-4 heteroatoms selected from N, O, and
 S, substituted with 0-3 R^{9e};

25

R^{9b}, at each occurrence, is independently selected from
 C₁₋₆ alkyl substituted with 0-3 R^{9e}, C₂₋₈ alkenyl
 substituted with 0-3 R^{9e}, C₂₋₈ alkynyl substituted
 with 0-3 R^{9e}, a (CH₂)_r-C₃₋₆ carbocyclic residue
 30 substituted with 0-2 R^{9e}, and a (CH₂)_r-5-6 membered

heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{9e};

R^{9d}, at each occurrence, is independently selected from H,
5 methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{9e},
C₃₋₆ alkenyl substituted with 0-3 R^{9e}, C₃₋₆ alkynyl
substituted with 0-3 R^{9e}, a C₃₋₁₀ carbocyclic residue
substituted with 0-3 R^{9e}, and a (CH₂)_{r-5-6} membered
heterocyclic system containing 1-4 heteroatoms
10 selected from N, O, and S, substituted with 0-3 R^{9e};

R^{9e}, at each occurrence, is independently selected from
C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆
cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃,
15 (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅
alkyl, (CH₂)_rNR^{9f}R^{9f}, and (CH₂)_rphenyl;

R^{9f}, at each occurrence, is independently selected from H,
C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

20 R¹⁰ is selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
alkynyl, (CRR)_rOH, (CRR)_rSH, (CRR)_rOR^{10d},
(CRR)_rS(O)_pR^{10d}, (CRR)_rC(O)R^{10b}, (CRR)_rNR^{10a}R^{10a},
(CRR)_rC(O)NR^{10a}R^{10a}, (CRR)_rC(O)NR^{10a}OR^{10d},
25 (CRR)_rSO₂NR^{10a}R^{10a}, (CRR)_rC(O)OR^{10d}, a (CRR)_r-C₃₋₁₀
carbocyclic residue substituted with 0-5 R^{10e}, and a
(CRR)_{r-5-10} membered heterocyclic system containing
1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{10e};

30

- alternatively, R^{10} and R^{11} join to form a C_{3-6} cycloalkyl substituted with 0-2 R^{10g} , a 5-6 membered ring lactam substituted with 0-2 R^{10g} , or a 5-6 membered ring lactone substituted with 0-2 R^{10g} ;
- 5 R^{10a} , at each occurrence, is independently selected from H, methyl, C_{2-6} alkyl substituted with 0-3 R^{10e} , C_{3-8} alkenyl substituted with 0-3 R^{10e} , C_{3-8} alkynyl substituted with 0-3 R^{10e} , $(CH_2)_r C_{3-6}$ cycloalkyl, a
- 10 $(CH_2)_r C_{3-10}$ carbocyclic residue substituted with 0-5 R^{10e} , and a $(CH_2)_r$ -5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{10e} ;
- 15 R^{10b} , at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-3 R^{10e} , C_{2-8} alkenyl substituted with 0-3 R^{10e} , C_{2-8} alkynyl substituted with 0-3 R^{10e} , a $(CH_2)_r C_{3-6}$ carbocyclic residue substituted with 0-2 R^{10e} , and a $(CH_2)_r$ -5-6 membered
- 20 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{10e} ;
- R^{10d} , at each occurrence, is independently selected from H, methyl, $-CF_3$, C_{2-6} alkyl substituted with 0-3
- 25 R^{10e} , C_{3-6} alkenyl substituted with 0-3 R^{10e} , C_{3-6} alkynyl substituted with 0-3 R^{10e} , a C_{3-10} carbocyclic residue substituted with 0-3 R^{10e} , and a $(CH_2)_r$ -5-6 membered heterocyclic system containing
- 30 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{10e} ;

R^{10e} , at each occurrence, is independently selected from
 C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-6}
 cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_r CF_3$,
 5 $(CH_2)_r OC_{1-5}$ alkyl, OH, $-O-C_{1-6}$ alkyl, SH, $(CH_2)_r SC_{1-5}$
 alkyl, $(CH_2)_r NR^{10f} R^{10f}$, and $(CH_2)_r$ phenyl;

R^{10f} , at each occurrence, is independently selected from
 H, C_{1-6} alkyl, and C_{3-6} cycloalkyl;

10

R^{10g} is selected from $(CHR)_q OH$, $(CHR)_q SH$, $(CHR)_q OR^{10d}$,
 $(CHR)_q S(O)_p R^{10d}$, $(CHR)_r C(O) R^{10b}$, $(CHR)_q NR^{10a} R^{10a}$,
 $(CHR)_r C(O) NR^{10a} R^{10a}$, $(CHR)_r C(O) NR^{10a} OR^{10d}$,
 $(CHR)_q SO_2 NR^{10a} R^{10a}$, $(CHR)_r C(O) OR^{10d}$, and a $(CHR)_r -C_{3-10}$
 15 carbocyclic residue substituted with 0-5 R^{10e} ;

R^{11} , is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}
 alkynyl, $(CRR)_r OH$, $(CRR)_r SH$, $(CRR)_r OR^{11d}$,
 $(CRR)_r S(O)_p R^{11d}$, $(CRR)_r C(O) R^{11b}$, $(CRR)_r NR^{11a} R^{11a}$,
 20 $(CRR)_r C(O) NR^{11a} R^{11a}$, $(CRR)_r C(O) NR^{11a} OR^{11d}$,
 $(CRR)_r SO_2 NR^{11a} R^{11a}$, $(CRR)_r C(O) OR^{11d}$, a $(CRR)_r -C_{3-10}$
 carbocyclic residue substituted with 0-5 R^{11e} , and a
 $(CRR)_r -5-10$ membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 25 substituted with 0-3 R^{11e} ;

R^{11a} , at each occurrence, is independently selected from
 H, methyl, C_{2-6} alkyl substituted with 0-3 R^{11e} , C_{3-8}
 alkenyl substituted with 0-3 R^{11e} , C_{3-8} alkynyl
 30 substituted with 0-3 R^{11e} , $(CH_2)_r C_{3-6}$ cycloalkyl, a
 $(CH_2)_r -C_{3-10}$ carbocyclic residue substituted with 0-5

R^{11e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{11e};

5 R^{11b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-3 R^{11e}, C₂₋₈ alkenyl substituted with 0-3 R^{11e}, C₂₋₈ alkynyl substituted with 0-3 R^{11e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{11e}, and a (CH₂)_r-5-6 membered
10 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{11e};

R^{11d}, at each occurrence, is independently selected from H, methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3
15 R^{11e}, C₃₋₆ alkenyl substituted with 0-3 R^{11e}, C₃₋₆ alkynyl substituted with 0-3 R^{11e}, a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{11e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S,
20 substituted with 0-3 R^{11e};

R^{11e}, at each occurrence, is independently selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃,
25 (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{11f}R^{11f}, and (CH₂)_rphenyl;

R^{11f}, at each occurrence, is independently selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

R^{12} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CRR)_qOH$, $(CRR)_qSH$, $(CRR)_qOR^{12d}$,
 $(CRR)_qS(O)_pR^{12d}$, $(CRR)_rC(O)R^{12b}$, $(CRR)_rNR^{12a}R^{12a}$,
 $(CRR)_rC(O)NR^{12a}R^{12a}$, $(CRR)_rC(O)NR^{12a}OR^{12d}$,
5 $(CRR)_qSO_2NR^{12a}R^{12a}$, $(CRR)_rC(O)OR^{12d}$, a $(CRR)_r-C_{3-10}$
carbocyclic residue substituted with 0-5 R^{12e} , and a
 $(CRR)_r-5-10$ membered heterocyclic system containing
1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{12e} ;
10
 R^{12a} , at each occurrence, is independently selected from
H, methyl, C_{2-6} alkyl substituted with 0-3 R^{12e} , C_{3-8}
alkenyl substituted with 0-3 R^{12e} , C_{3-8} alkynyl
substituted with 0-3 R^{12e} , $(CH_2)_rC_{3-6}$ cycloalkyl, a
15 $(CH_2)_r-C_{3-10}$ carbocyclic residue substituted with 0-5
 R^{12e} , and a $(CH_2)_r-5-10$ membered heterocyclic system
containing 1-4 heteroatoms selected from N, O, and
S, substituted with 0-3 R^{12e} ;
20
 R^{12b} , at each occurrence, is independently selected from
 C_{1-6} alkyl substituted with 0-3 R^{12e} , C_{2-8} alkenyl
substituted with 0-3 R^{12e} , C_{2-8} alkynyl substituted
with 0-3 R^{12e} , a $(CH_2)_r-C_{3-6}$ carbocyclic residue
substituted with 0-2 R^{12e} , and a $(CH_2)_r-5-6$ membered
25 heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{12e} ;

 R^{12d} , at each occurrence, is independently selected from
H, methyl, $-CF_3$, C_{2-6} alkyl substituted with 0-3
30 R^{12e} , C_{3-6} alkenyl substituted with 0-3 R^{12e} , C_{3-6}
alkynyl substituted with 0-3 R^{12e} , a C_{3-10}

carbocyclic residue substituted with 0-3 R^{12e} , and a
(CH₂)_r-5-6 membered heterocyclic system containing
1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{12e} ;

5

R^{12e} , at each occurrence, is independently selected from
C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆
cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃,
(CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅
10 alkyl, (CH₂)_rNR^{12f}R^{12f}, and (CH₂)_rphenyl;

R^{12f} , at each occurrence, is selected from H, C₁₋₆ alkyl,
and C₃₋₆ cycloalkyl;

15 R^{13} , at each occurrence, is independently selected from H,
and C₁₋₄alkyl substituted with 0-1 R^{13b} , -OH, -NH₂,
F, Cl, Br, I, -OR^{13a}, -N(R^{13a})₂, and C₁₋₄ alkyl
substituted with 0-3 R^{13b} ;

20 R^{13b} , at each occurrence, is independently selected from
-OH, -SH, -NR^{13c}R^{13c}, -C(O)NR^{13c}R^{13c}, and -NHC(O)R^{13c};

R^{13c} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;

25 R^{14} is independently selected from H, and C₁₋₄alkyl
substituted with 0-1 R^{14b} ;

R^{14b} , at each occurrence, is independently selected from
-OH, -SH, -NR^{14c}R^{14c}, -C(O)NR^{14c}R^{14c}, and -NHC(O)R^{14c};

30

R^{14c} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;

R¹⁶ is selected from H, C₁₋₄ alkyl substituted with 0-3 R^{16a}, and C₃₋₆ cycloalkyl substituted with 0-3 R^{16a};

R^{16a} is selected from C₁₋₄ alkyl, -OH, -SH, -NR^{16c}R^{16c},
5 -C(O)NR^{16c}R^{16c}, and -NHC(O)R^{16c};

R^{16c} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;

R¹⁷ is selected from H, C₁₋₄ alkyl, and C₃₋₄ cycloalkyl;

10

R¹⁸ is selected from H, C₁₋₄ alkyl, and C₃₋₄ cycloalkyl;

R¹⁹ is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl,
-C(O)H, and -C(O)-C₁₋₄alkyl;

15

R²⁴, at each occurrence, is independently selected from H
and C₁₋₄alkyl;

alternatively, two R²⁴s, along with the carbon atom to
20 which they are attached, join to form a C₃₋₆
carbocyclic ring;

R²⁵, at each occurrence, is independently selected from H,
C₁₋₄alkyl, OH, NH₂, -O-C₁₋₄ alkyl, NR^{25a}R^{25a},
25 C(O)NR^{25a}R^{25a}, NR^{25a}C(O)R^{25b}, NR^{25a}C(O)OR^{25d},
OC(O)NR^{25a}R^{25a}, and (CHR)_rC(O)OR^{25d};

alternatively, two R²⁵s, along with the carbon atom or
atoms to which they are attached, join to form a C₃₋₆
30 carbocyclic ring;

R^{25a}, at each occurrence, is independently selected from
H, and C₁₋₄ alkyl,

5 R^{25b}, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

R^{25d}, at each occurrence, is independently selected from
C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

10 R²⁶ is selected from C₁₋₄ alkyl;

n is selected from 0, 1, 2, and 3;

l is selected from 0 and 1;

15

m is selected from 0 and 1;

p, at each occurrence, is selected from 0, 1, or 2;

20 q, at each occurrence, is selected from 1, 2, 3, or 4;

r, at each occurrence, is selected from 0, 1, 2, 3, or 4;

s is selected from 0 and 1; and

25

t is selected from 1, 2 and 3.

[2] In another embodiment, the present invention
provides novel compounds of formula (I), wherein:

30

R¹⁶ is selected from H, C₁₋₄ alkyl substituted with 0-1

R^{16a}, wherein the alkyl is selected from methyl,

ethyl, propyl, i-propyl, butyl, i-butyl, and

s-butyl, and C₃₋₄ cycloalkyl substituted with 0-3

R^{16a} wherein the cycloalkyl is selected from cyclopropyl and cyclobutyl;

R^{16a} is selected from methyl, ethyl, propyl, i-propyl,
5 -OH, -SH, -NR^{16c}R^{16c}, -C(O)NR^{16c}R^{16c}, and -NHC(O)R^{16c};

R^{16c} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, cyclopropyl, cyclopentyl, and cyclohexyl; and

10 R¹⁷ is selected from H, methyl, ethyl, propyl, and i-propyl.

[3] In another embodiment, the present invention provides novel compounds of formula (I), wherein:

15

R⁹ and R¹¹ are H; and

R⁸ and R¹⁰ are independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, and cyclopropyl.

20

[4] In another embodiment, the present invention provides novel compounds of formula (I), wherein:

R³ is selected from (CRR)_qOH, (CRR)_qSH, (CRR)_qOR^{3d},
25 (CRR)_qS(O)_pR^{3d}, (CRR)_rC(O)R^{3b}, (CRR)_qNR^{3a}R^{3a},
(CRR)_rC(O)NR^{3a}R^{3a}, (CRR)_rC(O)NR^{3a}OR^{3d},
(CRR)_qSO₂NR^{3a}R^{3a}, (CRR)_rC(O)OR^{3d}, a (CRR)_r-C₃₋₁₀
carbocyclic residue substituted with 0-5 R^{3e}, and a
(CRR)_r-5-10 membered heterocyclic system containing
30 1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{3e} wherein the heterocyclic
system is selected from pyridinyl, thiophenyl,
furanyl, indazolyl, benzothiazolyl, benzimidazolyl,
benzothiophenyl, benzofuranyl, benzoxazolyl,
35 benzisoxazolyl, quinolinyl, isoquinolinyl,
imidazolyl, indolyl, indolinyl, isoindolyl,

isothiadiazolyl, isoxazolyl, piperidinyl,
 pyrrazolyl, pyrrolidinyl, tetrahydrofuranyl,
 tetrahydrothiophenyl, 1,2,4-triazolyl, 1,2,3-
 triazolyl, tetrazolyl, thiadiazolyl, thiazolyl,
 5 oxazolyl, pyrazinyl, and pyrimidinyl;

R^6 is selected from H, $(CRR)_qOH$, $(CRR)_qSH$, $(CRR)_qOR^{6d}$,
 $(CRR)_qS(O)_pR^{6d}$, $(CRR)_rC(O)R^{6b}$, $(CRR)_qNR^{6a}R^{6a}$,
 $(CRR)_rC(O)NR^{6a}R^{6a}$, $(CRR)_rC(O)NR^{6a}OR^{6d}$,
 10 $(CRR)_qSO_2NR^{6a}R^{6a}$, $(CRR)_rC(O)OR^{6d}$, a $(CRR)_r-C_{6-10}$
 carbocyclic residue substituted with 0-5 R^{6e} , and a
 $(CRR)_r-5-10$ membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-6 R^{6e} wherein the heterocyclic
 15 system is selected from pyridinyl, thiophenyl,
 furanyl, indazolyl, benzothiazolyl, benzimidazolyl,
 benzothiophenyl, benzofuranyl, benzoxazolyl,
 benzisoxazolyl, quinolinyl, isoquinolinyl,
 imidazolyl, indolyl, indolinyl, isoindolyl,
 20 isothiadiazolyl, isoxazolyl, piperidinyl,
 pyrrazolyl, pyrrolidinyl, tetrahydrofuranyl,
 tetrahydrothiophenyl, 1,2,4-triazolyl, 1,2,6-
 triazolyl, tetrazolyl, thiadiazolyl, thiazolyl,
 oxazolyl, pyrazinyl, and pyrimidinyl;

25

R^7 is H;

R^{12} is selected from H, methyl, ethyl, and propyl;

30 alternatively, R^3 and R^{12} join to form a C_{3-6} cycloalkyl
 substituted with 0-2 R^{3g} , a 5-6 membered lactam ring
 substituted with 0-2 R^{3g} , or a 5-6 membered lactone
 ring substituted with 0-2 R^{3g} ; and

35 $m + 1$ is equal to 1.

[5] In another embodiment, the present invention provides novel compounds of formula (I), wherein:

5 R¹ is selected from phenyl substituted with 0-3 R⁴ and a
5-10 membered heteroaryl system substituted with 0-3
R⁴, wherein the heteroaryl is selected from
benzimidazolyl, benzofuranyl, benzothiofuranyl,
benzoxazolyl, benzthiazolyl, benztriazolyl,
10 benztetrazolyl, benzisoxazolyl, benzisothiazolyl,
benzimidazalonyl, cinnolinyl, furanyl, imidazolyl,
indazolyl, indolyl, isoquinolinyl isothiazolyl,
isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl,
pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl,
15 quinazolinyl, quinolinyl, thiazolyl, thienyl, and
tetrazolyl;

R² is selected from phenyl substituted with 0-3 R⁵ and a
5-10 membered heteroaryl system containing 1-4
20 heteroatoms substituted with 0-3 R⁵, wherein the
heteroaryl system is selected from benzimidazolyl,
benzofuranyl, benzothiofuranyl, benzoxazolyl,
benzthiazolyl, benztriazolyl, benztetrazolyl,
benzisoxazolyl, benzisothiazolyl, benzimidazalonyl,
25 cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl,
isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl,
pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl,
pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl,
thiazolyl, thienyl, and tetrazolyl.

30

[6] In another embodiment, the present invention provides novel compounds of formula (I), wherein:

X is CHR¹⁶R¹⁷;

35

R^4 , at each occurrence, is selected from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CR'R')_rC_{3-6}$ cycloalkyl, Cl, Br, I, F, NO_2 , CN, $(CR'R')_rNR^{4a}R^{4a}$, $(CR'R')_rOH$, $(CR'R')_rOR^{4d}$, $(CR'R')_rSH$, $(CR'R')_rSR^{4d}$,
 5 $(CR'R')_rC(O)OH$, $(CR'R')_rC(O)R^{4b}$, $(CR'R')_rC(O)NR^{4a}R^{4a}$, $(CR'R')_rNR^{4f}C(O)R^{4b}$, $(CR'R')_rC(O)OR^{4d}$, $(CR'R')_rOC(O)R^{4b}$, $(CR'R')_rNR^{4f}C(O)OR^{4d}$, $(CR'R')_rOC(O)NR^{4a}R^{4a}$, $(CR'R')_rNR^{4a}C(O)NR^{4a}R^{4a}$, $(CR'R')_rS(O)_pR^{4b}$, $(CR'R')_rS(O)_2NR^{4a}R^{4a}$,
 10 $(CR'R')_rNR^{4f}S(O)_2R^{4b}$, $(CR'R')_rNR^{4f}S(O)_2NR^{4a}R^{4a}$, C_{1-6} haloalkyl, and $(CR'R')_r$ phenyl substituted with 0-3 R^{4e} ;

alternatively, two R^4 on adjacent atoms join to form
 15 $-O-(CH_2)-O-$;

R^{4a} , at each occurrence, is independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and
 20 a $(CH_2)_r-C_{3-6}$ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

R^{4b} , at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, a $(CH_2)_r-C_{3-6}$
 25 carbocyclic residue substituted with 0-3 R^{4e} , wherein the carbocyclic residue is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and a $(CH_2)_r-5-6$ membered heterocyclic system
 30 containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e} , wherein the heterocyclic system is selected from pyridinyl, thiophenyl, furanyl, indazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl,

benzisoaxazolyl, quinolinyl, isoquinolinyl,
 imidazolyl, indolyl, indolinyl, isoindolyl,
 isothiadiazolyl, isoxazolyl, piperidinyl,
 pyrrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl,
 5 tetrazolyl, thiadiazolyl, thiazolyl, oxazolyl,
 pyrazinyl, and pyrimidinyl;

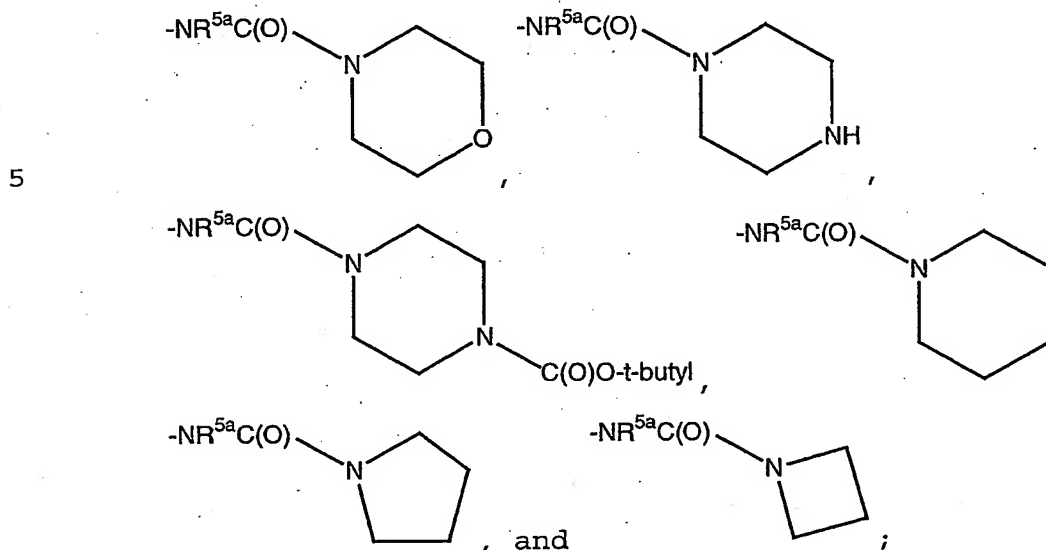
R^{4d} , at each occurrence, is selected from H, methyl, CF_3 ,
 ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl,
 10 t-butyl, pentyl, hexyl, allyl, propargyl, and a
 $(CH_2)_r-C_{3-6}$ carbocyclic residue selected from
 cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

R^{4e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8}
 15 alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, Cl, F,
 Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, SH,
 $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{4f}R^{4f}$, and $(CH_2)_rphenyl$;

R^{4f} , at each occurrence, is selected from H, methyl,
 20 ethyl, propyl, i-propyl, butyl, and cyclopropyl,
 cyclobutyl, and phenyl;

R^5 , at each occurrence, is selected from methyl, ethyl,
 propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl,
 25 pentyl, hexyl, $(CR'R')_rC_{3-6}$ cycloalkyl, Cl, Br, I, F,
 NO_2 , CN, $(CR'R')_rNR^{5a}R^{5a}$, $(CR'R')_rOH$, $(CR'R')_rOR^{5d}$,
 $(CR'R')_rSH$, $(CR'R')_rC(O)H$, $(CR'R')_rSR^{5d}$,
 $(CR'R')_rC(O)OH$, $(CR'R')_rC(O)R^{5b}$, $(CR'R')_rC(O)NR^{5a}R^{5a}$,
 $(CR'R')_rNR^{5f}C(O)R^{5b}$, $(CR'R')_rC(O)OR^{5d}$,
 30 $(CR'R')_rOC(O)R^{5b}$, $(CR'R')_rNR^{5f}C(O)OR^{5d}$,
 $(CR'R')_rOC(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{5a}C(O)NR^{5a}R^{5a}$,
 $(CR'R')_rNR^{7a}C(O)NR^{7a}R^{7a}$, $(CR'R')_rNR^{7a}C(O)O(CR'R')_rR^{7d}$,
 $(CR'R')_rS(O)_pR^{5b}$, $(CR'R')_rS(O)_2NR^{5a}R^{5a}$,
 $(CR'R')_rNR^{5f}S(O)_2R^{5b}$, C_{1-6} haloalkyl, and

(CHR')_rphenyl substituted with 0-3 R^{5e}, a (CRR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5c},



R^{5a}, at each occurrence, is independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-1 R^{5e}, wherein the carbocyclic residue is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and naphthyl;

15

20 R^{5b}, at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, a (CH₂)_r-C₃₋₆ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl; and

25 a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, wherein

the heterocyclic system is selected from pyridinyl, thiophenyl, furanyl, indazolyl, azetidiny, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, imidazolyl, indolyl, indolinyl, isoindolyl, isothiadiazolyl, isoxazolyl, morphlinyl, piperidinyl, pyrrolyl, 2,5-dihydropyrrolyl, pyrrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazinyl, and pyrimidinyl;

R^{5d}, at each occurrence, is selected from H, methyl, CF₃, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a (CH₂)_r-C₃₋₆ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

R^{5e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{4f}R^{4f}, and (CH₂)_rphenyl; and

R^{5f}, at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, and cyclopropyl, cyclobutyl, and phenyl.

[7] In another embodiment, the present invention provides novel compounds of formula (I), wherein:

R⁵ is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl, hexyl, CF₃, CF₂CF₃, CF₂H, OCF₃, Cl, Br, I, F, SCF₃, NR^{5a}R^{5a}, NHC(O)OR^{5a}, NHC(O)R^{5b}, and NHC(O)NHR^{5a}; and

R¹² is selected from H and methyl.

[8] In another embodiment, the present invention provides novel compounds of formula (I), wherein:

Z is -NC(O)-, -NHC(S)-, -NHC(O)NH-, -NHC(S)NH-, -NHSO₂-,
5 -NR¹⁹-CH₂-;

X is -CHR¹⁶NR¹⁷-;

R¹ is selected from phenyl substituted with 0-3 R⁴, and a
10 5-10 membered heteroaryl system substituted with 0-2
R⁴, wherein the heteroaryl is selected from indolyl,
and pyridyl;

R² is phenyl substituted with 0-2 R⁵;

15

R³ is selected from (CRR)_qOH, (CRR)_qOR^{3d}, (CH₂)_rC(O)OH,
(CH₂)_rC(O)NR^{3a}R^{3a}, (CHR)_rC(O)NR^{3a}OR^{3d}, (CH₂)_rC(O)R^{3b},
(CH₂)_rC(O)OR^{3d}, and (CH₂)-phenyl;

20 R^{3a} is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, s-butyl, t-butyl, allyl, CH₂CF₃,
C(CH₃)CH₂CH₂OH, cyclopropyl, 1-methylcyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and
benzyl;

25

R^{3b} is selected from pyrrolidinyl, pyrrolid-3-enyl, and
morpholinyl;

R^{3d} is selected from methyl, ethyl, propyl, i-propyl,
30 butyl, i-butyl, t-butyl and benzyl;

R is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, s-butyl, pentyl, neopentyl, phenyl
and benzyl;

35

R⁴ is selected from methyl, ethyl, propyl, i-propyl, butyl, ethylene, OCH₃, OCF₃, SCH₃, SO₂CH₃, Cl, F, Br, CN;

5 alternatively, two R⁴ join to form -O-(CH₂)-O-;

R⁶ is selected from H, methyl, ethyl, propyl, i-propyl, butyl, C(O)OCH₃, C(O)NHCH₂CH₃;

10 R⁷ is H;

R¹⁶ is selected from H and methyl;

R¹⁷ is selected from H and methyl;

15

m is 0 ;

l is 0

20 r is 0 or 1; and

q is 1.

[9] In another embodiment, the present invention
25 provides novel compounds of formula (I), wherein the compound is selected from:

N-[(3S)-1-{(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-
methyl]-2-hydroxy-pentyl}-2-oxo-pyrrolidin-3-yl]-3-
30 trifluoromethyl-benzamide;

1-[(3S)-1-{(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-
methyl]-2-hydroxy-pentyl}-2-oxo-pyrrolidin-3-yl]-3-
35 (3-trifluoromethylphenyl)-urea;

{2-[(3S)-1-[(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-ylcarbamoyl]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester;

5

2-Amino-N-[(3S)-1-[(1S, 2S)-1-[(2,4-dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-yl]-5-trifluoromethyl-benzamide;

10 3-Amino-N-[(3S)-1-[(1S, 2S)-1-[(2,4-dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-yl]-5-trifluoromethyl-benzamide; and

2-Amino-N-{(3S)-1-[(1S)-1-tert-butylcarbamoyl-2-(2,4-dimethyl-benzylamino)-ethyl]-2-oxo-pyrrolidin-3-yl}-5-trifluoromethyl-benzamide.

15

In another embodiment, the present invention is directed to a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula (I).

20

In another embodiment, the present invention is directed to a method for modulation of chemokine or chemokine receptor activity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

25

In another embodiment, the present invention is directed to a method for modulation of MCP-1, MCP-2, MCP-3 and MCP-4, and MCP-5 activity that is mediated by the CCR2 receptor comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

30

35

In another embodiment, the present invention is directed to a method for modulation of MCP-1 activity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating disorders, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), said disorders being selected from osteoarthritis, aneurism, fever, cardiovascular effects, Crohn's disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerularnephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

In another embodiment, the present invention is directed to a method for treating disorders, of Formula (I), wherein said disorders being selected from psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerularnephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

In another embodiment, the present invention is directed to a method for treating disorders, of Formula (I), wherein said disorders being selected from alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerularnephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

In another embodiment, the present invention is directed to a method for treating disorders, of Formula (I), wherein said disorders being selected from asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

In another embodiment, the present invention is directed to a method for treating rheumatoid arthritis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating multiple sclerosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating atherosclerosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating asthma, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating restinosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating organ transplatation, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

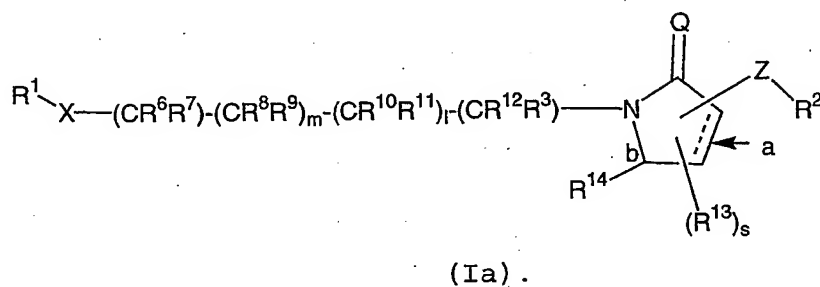
In another embodiment, the present invention is directed to a method for treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the present invention is directed to a method for treating inflammatory diseases, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I).

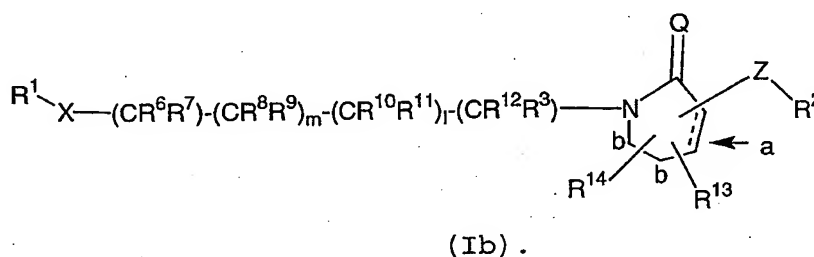
In another embodiment, the present invention is directed to a method for modulation of CCR2 activity comprising administering to a patient in need thereof a

therapeutically effective amount of a compound of Formula (I).

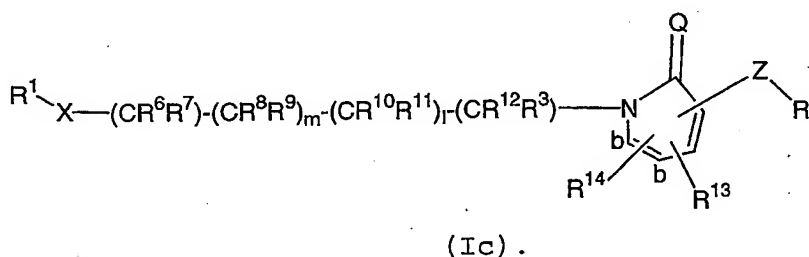
In another embodiment, the present invention is directed to a compound of formula (Ia)



In another embodiment, the present invention is directed to a compound of formula (Ib)



In another embodiment, the present invention is directed to a compound of formula (Ic)



In another embodiment, Z is -NHC(O)-.

In another embodiment, X is -CHR¹⁶NR¹⁷-; and

R^{16} is selected from H, C_{1-4} alkyl substituted with 0-1 R^{16a} , wherein the alkyl is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, and s-butyl, and C_{3-4} cycloalkyl substituted with 0-3 R^{16a} wherein the cycloalkyl is selected from cyclopropyl and cyclobutyl;

R^{16a} is selected from methyl, ethyl, propyl, i-propyl, -OH, -SH, $-NR^{16c}R^{16c}$, $-C(O)NR^{16c}R^{16c}$, and $-NHC(O)R^{16c}$; and

R^{17} is selected from H, methyl, ethyl, propyl, and i-propyl.

In another embodiment, R^7 , R^8 , R^9 , and R^{11} are H;

R^{10} is selected from H and methyl;

R^{16} is selected from H and methyl;

R^{17} is selected from H and methyl;

m is 0 or 1; and

l is 0 or 1.

In another embodiment, R^3 is selected from $(CRR)_qOH$, $(CRR)_qSH$, $(CRR)_qOR^{3d}$, $(CRR)_qS(O)_pR^{3d}$, $(CRR)_rC(O)R^{3b}$, $(CRR)_qNR^{3a}R^{3a}$, $(CRR)_rC(O)NR^{3a}R^{3a}$, $(CRR)_rC(O)NR^{3a}OR^{3d}$, $(CRR)_qSO_2NR^{3a}R^{3a}$, $(CRR)_rC(O)OR^{3d}$, a $(CRR)_r-C_{3-10}$ carbocyclic residue substituted with 0-5 R^{3e} , and a $(CRR)_r-5-10$ membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3e} wherein the heterocyclic system is selected from pyridinyl, thiophenyl,

furanyl, indazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, imidazolyl, indolyl, indolinyl, isoindolyl, isothiadiaazolyl, isoxazolyl, piperidinyl, pyrrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, thiadiaazolyl, thiazolyl, oxazolyl, pyrazinyl, and pyrimidinyl;

10 alternatively, R^3 and R^{12} join to form a C_{3-6} cycloalkyl substituted with 0-2 R^{3g} , a C_{5-6} lactam substituted with 0-2 R^{3g} , or a C_{5-6} lactone substituted with 0-2 R^{3g} .

15 In another embodiment, R^3 is selected from $(CRR)_qOH$, $(CH_2)_rC(O)OH$, $(CH_2)_rC(O)NR^{3a}R^{3a}$, $(CHR)_rC(O)NR^{3a}OR^{3d}$, $(CH_2)_rC(O)R^{3b}$, $(CH_2)_rC(O)OR^{3d}$, and (CH_2) -phenyl.

20 In another embodiment, R^3 is H and R^6 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CRR)_qOH$, $(CRR)_qSH$, $(CRR)_qOR^{6d}$, $(CRR)_qS(O)_pR^{6d}$, $(CRR)_rC(O)R^{6b}$, $(CRR)_rNR^{6a}R^{6a}$, $(CRR)_rC(O)NR^{6a}R^{6a}$, $(CRR)_rC(O)NR^{6a}OR^{6d}$, $(CRR)SO_2NR^{6a}R^{6a}$, $(CRR)_rC(O)OR^{6d}$, a $(CRR)_r-C_{3-10}$ carbocyclic residue substituted with 0-5 R^{6e} , and a
25 $(CRR)_r-5-10$ membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e} .

In another embodiment, R^6 is selected from H, $(CRR)_qOH$,
30 $(CRR)_qSH$, $(CRR)_qOR^{6d}$, $(CRR)_qS(O)_pR^{6d}$, $(CRR)_rC(O)R^{6b}$, $(CRR)_qNR^{6a}R^{6a}$, $(CRR)_rC(O)NR^{6a}R^{6a}$, $(CRR)_rC(O)NR^{6a}OR^{6d}$, $(CRR)_qSO_2NR^{6a}R^{6a}$, $(CRR)_rC(O)OR^{6d}$, a $(CRR)_r-C_{6-10}$ carbocyclic residue substituted with 0-5 R^{6e} , and a

(CRR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-6 R^{6e} wherein the heterocyclic system is selected from pyridinyl, thiophenyl, furanyl, indazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, imidazolyl, indolyl, indolinyl, isoindolyl, isothiadiazolyl, isoxazolyl, piperidinyl, pyrrazolyl, 1,2,4-triazolyl, 1,2,6-triazolyl, tetrazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazinyl, and pyrimidinyl.

In another embodiment, R¹ is selected from phenyl substituted with 0-3 R⁴ and a 5-10 membered heteroaryl system substituted with 0-3 R⁴, wherein the heteroaryl is selected from benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl, isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, thiazolyl, thienyl, and tetrazolyl.

In another embodiment, R¹ is selected from phenyl substituted with 0-2 R⁴, indolyl, and pyridyl.

In another embodiment, R² is selected from phenyl substituted with 0-3 R⁵ and a 5-10 membered heteroaryl system containing 1-4 heteroatoms substituted with 0-3 R⁵, wherein the heteroaryl system is selected from benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl,

benzthiazolyl, benztriazolyl, benztetrazolyl,
 benzisoxazolyl, benzisothiazolyl, benzimidazalonyl,
 cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl,
 isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl,
 5 pyrazinyl, pyrazolyl, pyridazinyl, pyridyl,
 pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl,
 quinolinyl, thiazolyl, thienyl, and tetrazolyl.

In another embodiment, R² is phenyl substituted with 0-2
 10 R⁵.

In another embodiment, R⁴, at each occurrence, is
 selected from C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl,
 (CR'R')_xC₃₋₆ cycloalkyl, Cl, Br, I, F, NO₂, CN,
 15 (CR'R')_xNR^{4a}R^{4a}, (CR'R')_xOH, (CR'R')_xOR^{4d}, (CR'R')_xSH,
 (CR'R')_xSR^{4d}, (CR'R')_xC(O)OH, (CR'R')_xC(O)R^{4b},
 (CR'R')_xC(O)NR^{4a}R^{4a}, (CR'R')_xNR^{4f}C(O)R^{4b},
 (CR'R')_xC(O)OR^{4d}, (CR'R')_xOC(O)R^{4b},
 (CR'R')_xNR^{4f}C(O)OR^{4d}, (CR'R')_xOC(O)NR^{4a}R^{4a},
 20 (CR'R')_xNR^{4a}C(O)NR^{4a}R^{4a}, (CR'R')_xS(O)_pR^{4b},
 (CR'R')_xS(O)₂NR^{4a}R^{4a}, (CR'R')_xNR^{4f}S(O)₂R^{4b},
 (CR'R')_xNR^{4f}S(O)₂NR^{4a}R^{4a}, C₁₋₆ haloalkyl, and
 (CR'R')_xphenyl substituted with 0-3 R^{4e};

25 alternatively, two R⁴ on adjacent atoms join to form
 -O-(CH₂)-O-;

R^{4a}, at each occurrence, is independently selected from H,
 methyl, ethyl, propyl, i-propyl, butyl, s-butyl,
 30 i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl,
 and a (CH₂)_x-C₃₋₆ carbocyclic residue selected from
 cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

- R^{4b} , at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, a $(CH_2)_r-C_{3-6}$ carbocyclic residue substituted with 0-3 R^{4e} , wherein the carbocyclic residue is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and a $(CH_2)_r-5-6$ membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e} , wherein the heterocyclic system is selected from pyridinyl, thiophenyl, furanyl, indazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, imidazolyl, indolyl, indolinyl, isoindolyl, isothiadiazolyl, isoxazolyl, piperidinyl, pyrrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazinyl, and pyrimidinyl;
- R^{4d} , at each occurrence, is selected from H, methyl, CF_3 , ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a $(CH_2)_r-C_{3-6}$ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
- R^{4e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{4f}R^{4f}$, and $(CH_2)_r$ phenyl;
- R^{4f} , at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, and cyclopropyl, cyclobutyl, and phenyl.

In another embodiment, R^4 is selected from methyl, ethyl, propyl, i-propyl, butyl, ethylene, OCH_3 , OCF_3 , SCH_3 , SO_2CH_3 , Cl, F, Br, and CN;

5 alternatively, two R^4 join to form $-O-(CH_2)-O-$.

In another embodiment, R^5 , at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl,
 10 $(CR'R')_rC_{3-6}$ cycloalkyl, Cl, Br, I, F, NO_2 , CN, $(CR'R')_rNR^{5a}R^{5a}$, $(CR'R')_rOH$, $(CR'R')_rOR^{5d}$, $(CR'R')_rSH$, $(CR'R')_rC(O)H$, $(CR'R')_rSR^{5d}$, $(CR'R')_rC(O)OH$, $(CR'R')_rC(O)R^{5b}$, $(CR'R')_rC(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{5f}C(O)R^{5b}$, $(CR'R')_rC(O)OR^{5d}$,
 15 $(CR'R')_rOC(O)R^{5b}$, $(CR'R')_rNR^{5f}C(O)OR^{5d}$, $(CR'R')_rOC(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{5a}C(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{7a}C(O)NR^{7a}R^{7a}$, $(CR'R')_rNR^{7a}C(O)O(CR'R')_rR^{7d}$, $(CR'R')_rS(O)_pR^{5b}$, $(CR'R')_rS(O)_2NR^{5a}R^{5a}$, $(CR'R')_rNR^{5f}S(O)_2R^{5b}$, C_{1-6} haloalkyl, and
 20 $(CHR')_r$ phenyl substituted with 0-3 R^{5e} ;

alternatively, two R^5 on adjacent atoms join to form
 $-O-(CH_2)-O-$;

25 R^{5a} , at each occurrence, is independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a $(CH_2)_r-C_{3-6}$ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

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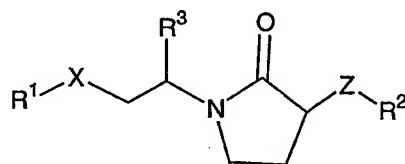
R^{5b} , at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a $(CH_2)_r-C_{3-6}$

carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

- 5 R^{5d} , at each occurrence, is selected from H, methyl, CF_3 , ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a $(CH_2)_r-C_{3-6}$ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
- 10 R^{5e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{4f}R^{4f}$, and $(CH_2)_r$ phenyl; and
- 15 R^{5f} , at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, and cyclopropyl, cyclobutyl, and phenyl.

In another embodiment, R^5 is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl, hexyl, CF_3 , CF_2CF_3 , CF_2H , OCF_3 , Cl, Br, I, F, SCF_3 , $NR^{5a}R^{5a}$, $NHC(O)OR^{5a}$, $NHC(O)R^{5b}$, and $NHC(O)NHR^{5a}$.

In another embodiment, the present invention is directed to compounds of Formula (Ib),



(Ib)

or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from a bond, $-NR^{18}C(O)-$, $-NR^{18}C(S)-$,
 $-NR^{18}C(O)NH-$, and $-NR^{18}C(S)NH-$;

X is selected from $-NR^{17}-$ and $-CHR^{16}NR^{17}-$.

5

In another embodiment, the present invention is directed the use of a compound of Formula (I) in the preparation of a medicament for the treatment of osteoarthritis, aneurism, fever, cardiovascular effects,
10 Crohn's disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis,
15 systemic lupus erythematosus, nephrotoxic serum nephritis, glomerularnephritis, asthma, multiple sclerosis, artherosclerosis, and rheumatoid arthritis.

In another embodiment, the present invention is
20 directed to a compound of formula (I) for use in therapy.

The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all
25 combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional even more preferred embodiments of the present invention.
30 Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing
5 an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric
10 isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may
15 be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

20 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom or ring is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable
25 compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^a) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its
30 definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^a, then said group may optionally be substituted with up to two R^a groups and R^a at each occurrence is selected independently from the definition of R^a. Also,
35 combinations of substituents and/or variables are

permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "C₁₋₈ alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. C₁₋₈ alkyl, is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, and C₈ alkyl groups. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, and the like. "C₃₋₆ cycloalkyl" is intended to include saturated ring groups having the specified number of carbon atoms in the ring, including mono-, bi-, or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl in the case of C₇ cycloalkyl. C₃₋₆ cycloalkyl,

is intended to include C₃, C₄, C₅, and C₆ cycloalkyl groups

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups, for example CF₃, having the specified number of carbon atoms, substituted with 1 or more halogen (for example -C_vF_w where v = 1 to 3 and w = 1 to (2v+1)).

As used herein, the term "5-6-membered cyclic ketal" is intended to mean 2,2-disubstituted 1,3-dioxolane or 2,2-disubstituted 1,3-dioxane and their derivatives.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,; [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and

sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. As used herein, the term "aromatic heterocyclic system" or "heteroaryl" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and is aromatic in nature.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidinyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 4-piperidinyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolonyl, carbazolyl, 4aH-carbazolyl, β -carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,

oxazolidinyl, oxazolyl, oxazolidinylperimidinyl,
phenanthridinyl, phenanthrolinyl, phenarsazinyl,
phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,
phthalazinyl, piperazinyl, piperidinyl, pteridinyl,
5 piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl,
pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl,
pyridazinyl, pyridooxazole, pyridoimidazole,
pyridothiazole, pyridinyl, pyridyl, pyrimidinyl,
pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl,
10 quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl,
carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl,
tetrahydroquinolinyl, tetrahydropyrimidin-2-onyl
6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-
thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,
15 thianthrenyl, thiazolyl, thienyl, thienothiazolyl,
thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl,
1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-
triazolyl, tetrazolyl, and xanthenyl. In another aspect
of the invention, the heterocycles include, but are not
20 limited to, pyridinyl, thiophenyl, furanyl, indazolyl,
azetidyl, benzothiazolyl, benzimidazolyl,
benzothiophenyl, benzofuranyl, benzoxazolyl,
benzisoxazolyl, quinolinyl, isoquinolinyl, imidazolyl,
indolyl, indolinyl, isoindolyl, isothiadiazolyl,
25 isoxazolyl, morphlinyl, piperidinyl, pyrrolyl, 2,5-
dihydropyrrolyl, pyrrazolyl, 1,2,4-triazolyl, 1,2,3-
triazolyl, tetrazolyl, thiadiazolyl, thiazolyl, oxazolyl,
pyrazinyl, and pyrimidinyl. Also included are fused ring
and spiro compounds containing, for example, the above
30 heterocycles.

Examples of heteroaryls are 1H-indazole, 2H,6H-
1,5,2-dithiazinyl, 4aH-carbazole, 4H-quinoliziny, 6H-
1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl,
benzofuranyl, benzothiofuranyl, benzothiophenyl,
35 benzoxazolyl, benzthiazolyl, benztriazolyl,
benztetrazolyl, benzisoxazolyl, benzisothiazolyl,

benzimidazalonyl, carbazolyl, 4aH-carbazolyl,
β-carboliny, chromanyl, chromenyl, cinnoliny,
decahydroquinoliny, 2H,6H-1,5,2-dithiaziny,
dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl,
5 imidazolidiny, imidazoliny, imidazolyl, 1H-indazolyl,
indolenyl, indoliny, indoliziny, indolyl,
isobenzofuranyl, isochromanyl, isoindazolyl,
isoindoliny, isoindolyl, isoquinoliny (benzimidazolyl),
isothiazolyl, isoxazolyl, morpholiny, naphthyridiny,
10 octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl,
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
oxazolidiny, oxazolyl, oxazolidiny, perimidiny,
phenanthridiny, phenanthroliny, phenarsaziny,
phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny,
15 phthalaziny, piperaziny, piperidiny, pteridiny,
piperidony, 4-piperidony, pteridiny, puriny, pyranly,
pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl,
pyridaziny, pyridooxazole, pyridoimidazole,
pyridothiazole, pyridiny, pyridyl, pyrimidiny,
20 pyrrolidiny, pyrroliny, pyrroly, quinazoliny,
quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny,
carboliny, tetrahydrofuranyl, tetrahydroisoquinoliny,
tetrahydroquinoliny, 6H-1,2,5-thiadiaziny, 1,2,3-
thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
25 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl,
thienothiazolyl, thienooxazolyl, thienoimidazolyl,
thiophenyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl,
1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, and
xanthenyl. In another aspect of the invention, examples
30 of heteroaryls are benzimidazolyl, benzofuranyl,
benzothiofuranyl, benzoxazolyl, benzthiazolyl,
benztriazolyl, benztetrazolyl, benzisoxazolyl,
benzisothiazolyl, benzimidazalonyl, cinnoliny, furanyl,
imidazolyl, indazolyl, indolyl, isoquinoliny
35 isothiazolyl, isoxazolyl, oxazolyl, pyraziny, pyrazolyl,
pyridaziny, pyridyl, pyridiny, pyrimidiny, pyrroly,

quinazolinyl, quinolinyl, thiazolyl, thienyl, and tetrazolyl.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound

which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate
5 base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed.,
10 Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of
15 the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded
20 carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the
25 modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered
30 to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of
35 the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or in combination with other active ingredients effective to inhibit MCP-1 or effective to treat or prevent inflammatory disorders.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

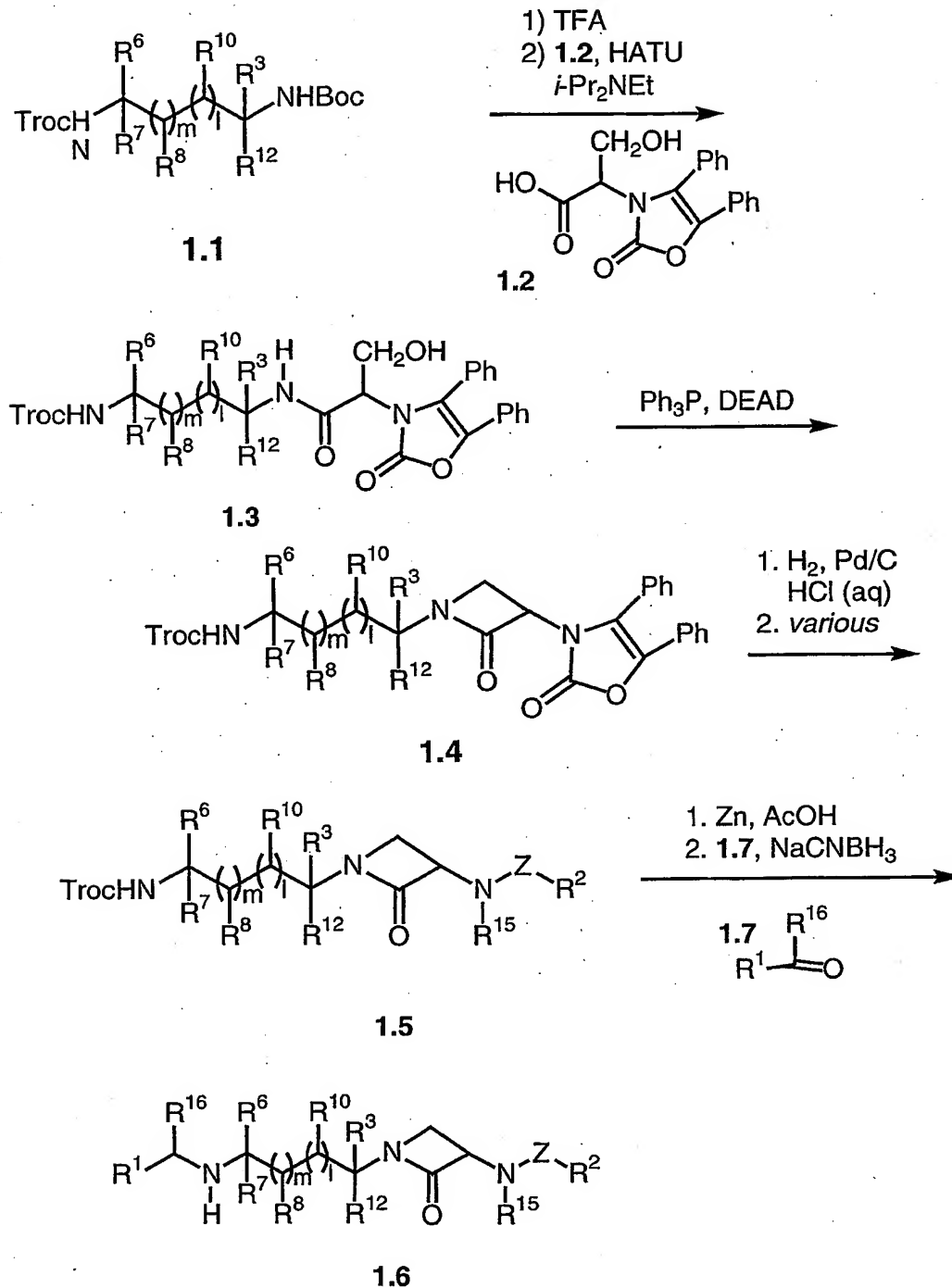
The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents

appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed
5 reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is
10 understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be
15 readily apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It
20 will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An
25 authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Third Edition, Wiley and Sons, 1999).

Compounds of formula 1.6, which contain a four-
30 membered lactam, are derived from compounds of formula 1.1, the syntheses of which have been described previously (P. H. Carter, R. J. Cherney, WO-PCT 0250019, 2002, the contents of which are hereby incorporated by

reference). As shown in Scheme 1, acid-mediated Boc removal, peptide coupling with the known serine derivative 1.2, and cyclization under Mitsunobu conditions (see GM Salituro and CA Townsend *J. Am. Chem. Soc.* 1990, 112, 760 - 770) provides the beta-lactam 1.4 from carbamate 1.1. Removal of the Ox protecting group (see GM Salituro and CA Townsend *J. Am. Chem. Soc.* 1990, 112, 760 - 770) provides a primary amine, which can be conjugated in a variety of ways well known to one skilled in the art. For example, reaction with an acid chloride will form an amide (Z = -CO-) and reaction with an isocyanate will form a urea (Z = -CONH-). The resultant compounds 1.5 are transformed to compounds 1.6 through deprotection and reductive amination. If desired, compounds of formula 1.6 can be alkylated via a second reductive amination (not illustrated).

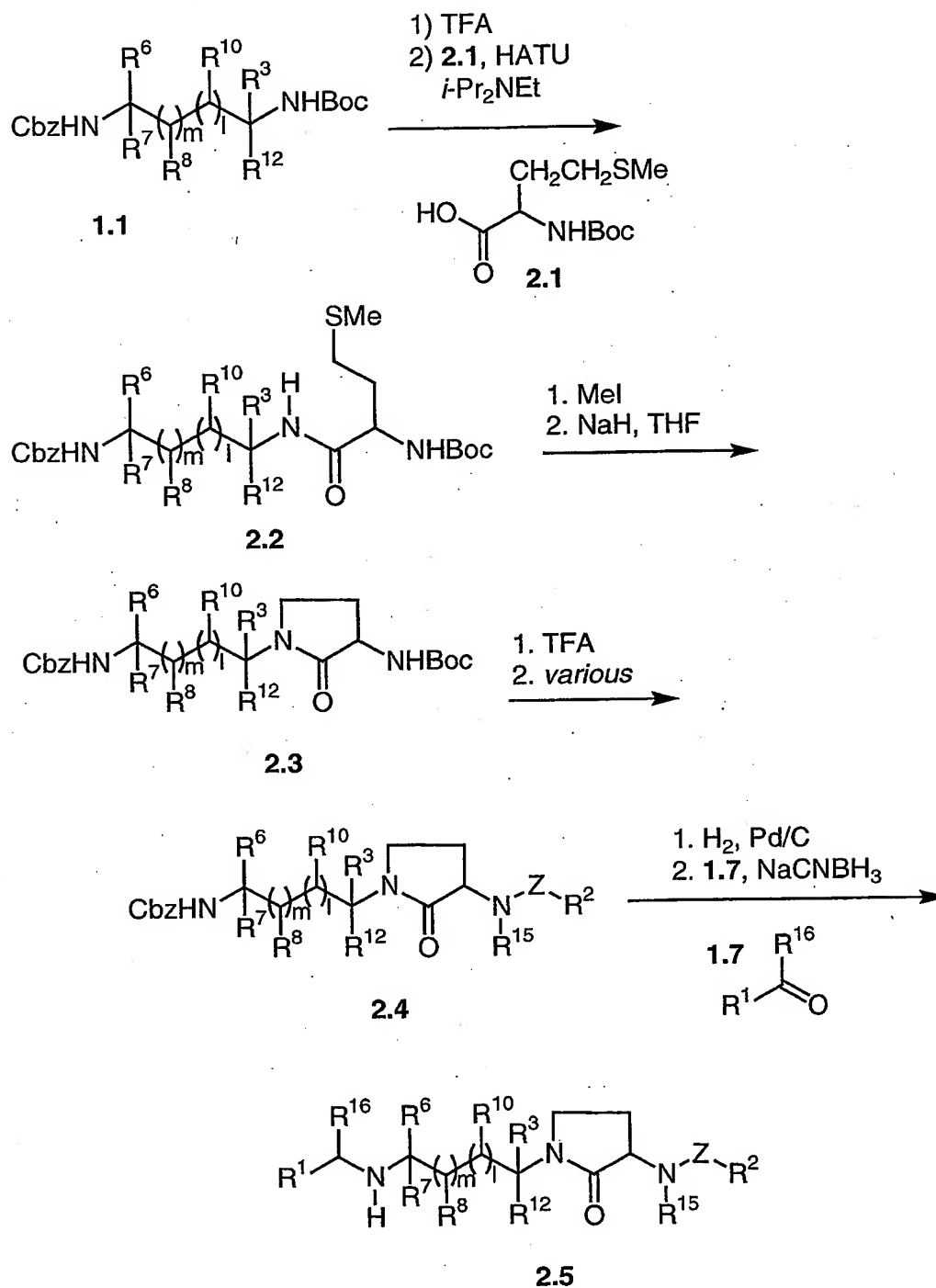
Scheme 1



Compounds of formula 2.5, which contain a five-membered lactam, are synthesized as shown in Scheme 2. Acid-mediated Boc removal, peptide coupling with the known methionine derivative 2.1, sulfur alkylation, and

intramolecular amide alkylation under basic conditions (Freidinger et al., *J. Org. Chem.* 1982, 47, 104) provides the gamma-lactam 2.3 from carbamate 1.1. Removal of the Boc protecting group provides a primary amine, which can
5 be conjugated in a variety of ways well known to one skilled in the art. For example, reaction with an acid chloride will form an amide ($Z = -CO-$) and reaction with, an isocyanate will form a urea ($Z = -CONH-$). The resultant compounds 2.4 are transformed to compounds 2.5
10 through deprotection and reductive amination. If desired, compounds of formula 2.5 can be alkylated via a second reductive amination (not illustrated).

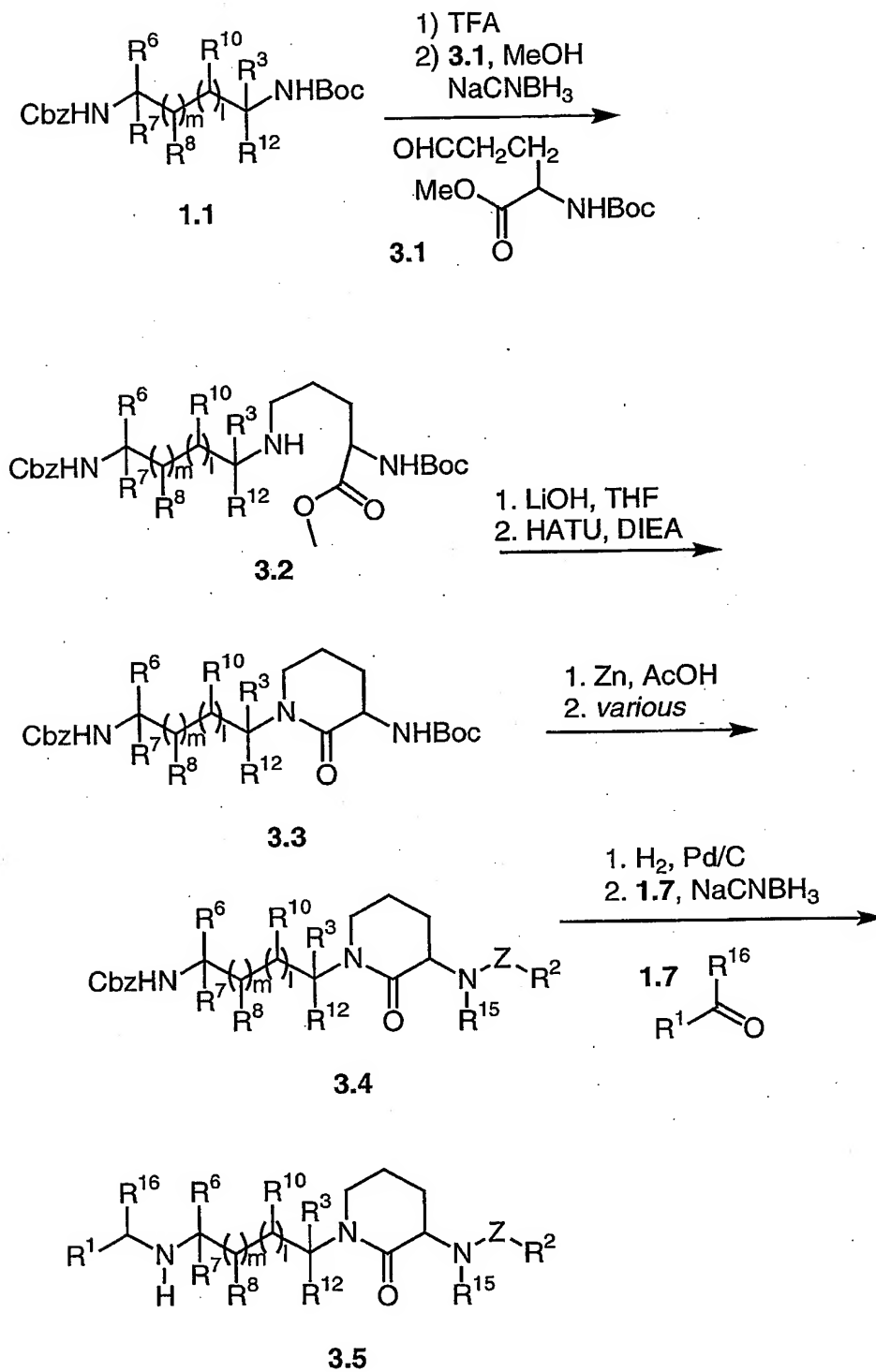
Scheme 2



Compounds of formula 3.5, which contain a six-membered lactam, are synthesized as shown in Scheme 3. Acid-mediated Boc removal, reductive amination with the

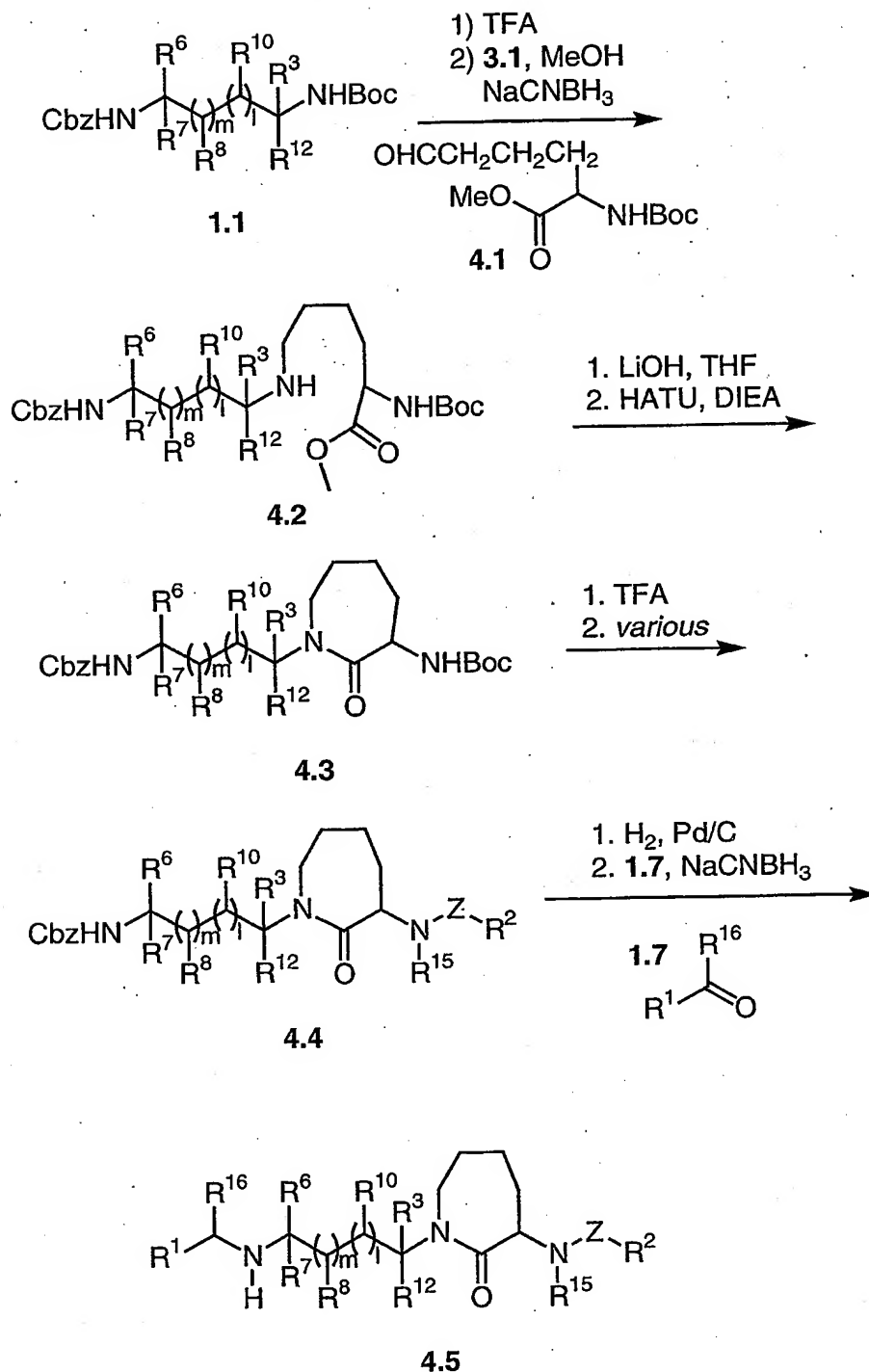
known glutamic acid derivative 3.1 (X. Zhang, W. Han, WO PCT 0164678, 2001), ester hydrolysis, and intramolecular amide formation provides the delta-lactam 3.3 from carbamate 1.1. Removal of the Boc protecting group
5 provides a primary amine, which can be conjugated in a variety of ways well known to one skilled in the art. For example, reaction with an acid chloride will form an amide (Z = -CO-) and reaction with an isocyanate will form a urea (Z = -CONH-). The resultant compounds 3.4
10 are transformed to compounds 3.5 through deprotection and reductive amination. If desired, compounds of formula 3.5 can be alkylated via a second reductive amination (not illustrated).

Scheme 3



Compounds of formula 4.5, which contain a seven-membered lactam, are synthesized as shown in Scheme 4. Acid-mediated Boc removal, reductive amination with the homoglutamic acid derivative 4.1 (prepared through a trivial modification of the procedure outlined in Kenji Mori, et al., *Tetrahedron* 1985, 41, 5307 - 5311), ester hydrolysis, and intramolecular amide formation provides the lactam 4.3 from carbamate 1.1. Removal of the Boc protecting group provides a primary amine, which can be conjugated in a variety of ways well known to one skilled in the art. For example, reaction with an acid chloride will form an amide (Z = -CO-) and reaction with an isocyanate will form a urea (Z = -CONH-). The resultant compounds 4.4 are transformed to compounds 4.5 through deprotection and reductive amination. If desired, compounds of formula 4.5 can be alkylated via a second reductive amination (not illustrated).

Scheme 4



Other features of the invention will become apparent in the course of the following descriptions of exemplary

embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

5

Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or
10 milligrams, "mL" for milliliter or milliliters, "¹H" for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin
15 layer chromatography, "v/v" for volume to volume ratio. "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

20 N-[(3S)-1-{(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl}-2-oxo-pyrrolidin-3-yl]-3-trifluoromethyl-benzamide

(1a) A solution of [1S, 2S]-[1-(Benzyloxycarbonylamino-methyl)-2-hydroxy-pent-3-ynyl]-carbamic acid tert-butyl
25 ester (1.19 g, 3.29 mmol, prepared as described in WO PCT 0250019) was dissolved in CH₂Cl₂ (20 mL) and treated with TFA (10 mL). The solution was stirred for 3 h and then concentrated in vacuo. The residue was dissolved in
30 CH₂Cl₂ and concentrated in vacuo; this procedure was repeated. The residue was dissolved in CH₂Cl₂ (30 mL). The resultant solution was charged sequentially with N,N-diisopropylethylamine (2.3 mL, 13.2 mmol), HOBt (466

mg, 3.45 mmol), N-Boc methionine (820 mg, 3.29 mmol), and BOP (1.53 g, 3.45 mmol). The reaction was stirred for 12 h and partitioned between EtOAc and sat. NH_4Cl . The organic phase was washed with sat. NaHCO_3 and brine, and
5 then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford [2*S*, 3*S*]-[2-[(2*S*)-(2-tert-butoxycarbonylamino-4-methylsulfanyl-butyrylamino)]-3-hydroxy-hex-4-ynyl]-carbamic acid benzyl ester (1.27 g, 78% yield). MS found:
10 $(\text{M} + \text{Na})^+ = 516.3$.

(1b) The compound (2*S*, 3*S*)-[2-[(2*S*)-(2-tert-butoxycarbonylamino-4-methylsulfanyl-butyrylamino)]-3-hydroxy-hex-4-ynyl]-carbamic acid benzyl ester (1.27 g,
15 2.6 mmol) was dissolved in 10:1 iodomethane/EtOAc (22 mL). The resultant solution was stirred for 65 h at RT, at which point a two-phase mixture had evolved. The mixture was treated with 1:1 CHCl_3 /EtOAc until dissolution was achieved, and then the resultant solution
20 was concentrated in vacuo. The residue was redissolved in 1:1 CHCl_3 /EtOAc and concentrated in vacuo; this procedure was repeated to give the salt as a yellow solid. This material was dissolved in THF (45 mL). The resultant solution was cooled to 0 °C, treated with
25 sodium hydride (310 mg, 12.9 mmol), and stirred for 2 h at 0 °C. The reaction was quenched with sat. NH_4Cl and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by
30 flash chromatography to afford {(3*S*)-1-[(1*S*, 2*S*)-1-(benzyloxycarbonylamino-methyl)-2-hydroxy-pent-3-ynyl]-2-

oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (913 mg, 79% yield). MS found: $(M + Na)^+ = 468.4$.

- (1c) The compound {(3*S*)-1-[(1*S*, 2*S*)-1-(benzyloxycarbonylamino-methyl)-2-hydroxy-pent-3-ynyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (913 mg, 2.05 mmol) was dissolved in MeOH (20 mL). The resultant solution was charged with 5% Pd/C, Degussa style (500 mg), stirred under H₂ (1 atm) for 12 h at RT, filtered, and concentrated in vacuo. The residue was redissolved in MeOH (20 mL). The resultant solution was charged sequentially with 2,4-dimethylbenzaldehyde and sodium cyanoborohydride, stirred for 12 h at RT, quenched with sat. NaHCO₃, and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was redissolved in 2:1 THF/H₂O (30 mL). The resultant solution was charged with triethylamine (1.1 mL, 8.2 mmol) and dibenzylidicarbonate (700 mg, 2.46 mmol), stirred for 12 h at RT, quenched with sat. NH₄Cl, and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified via flash chromatography to afford {(3*S*)-1-[(1*S*, 2*S*)-1-{[benzyloxycarbonyl-(2,4-dimethyl-benzyl)-amino]-methyl}-2-hydroxy-pent-3-ynyl]}-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (1.16 g, 85% yield). MS found: $(M + H)^+ = 568.4$.

- (1d) A solution of {(3*S*)-1-[(1*S*, 2*S*)-1-{[benzyloxycarbonyl-(2,4-dimethyl-benzyl)-amino]-methyl}-2-hydroxy-pent-3-ynyl]}-2-oxo-pyrrolidin-3-yl}-carbamic

acid tert-butyl ester (1.16 g, 1.74 mmol) was dissolved in CH₂Cl₂ (16 mL) and treated with TFA (8 mL). The solution was stirred for 3 h and then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ and concentrated in vacuo; this procedure was repeated. A portion (0.22 mmol) of the product amine was dissolved in CH₂Cl₂ (4 mL). The resultant solution was charged sequentially with N, N-diisopropylethylamine (0.16 mL, 0.88 mmol), 4-dimethylaminopyridine (24 mg, 0.22 mmol), meta-trifluoromethylbenzoic acid (41 mg, 0.22 mmol), and BOP (96 mg, 0.22 mmol). The reaction was stirred for 12 h and partitioned between EtOAc and sat. NH₄Cl. The organic phase was washed with sat. NaHCO₃ and brine, and then dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was dissolved in MeOH (6 mL). The resultant solution was charged with 5% Pd/C, Degussa style (50 mg), stirred under H₂ (1 atm) for 12 h at RT, filtered, and concentrated in vacuo. The residue was purified by reverse-phase HPLC to afford the title compound as a white powder after lyophilization. MS found: (M + H)⁺ = 506.6.

Example 2

1-[(3S)-1-[(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-yl]-3-(3-trifluoromethylphenyl)-urea

(2a) A solution of {(3S)-1-[(1S, 2S)-1-[[benzyloxycarbonyl-(2,4-dimethyl-benzyl)-amino]-methyl]-2-hydroxy-pent-3-ynyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (1.16 g, 1.74 mmol, see procedure 1c above) was dissolved in CH₂Cl₂ (16 mL) and treated with

TFA (8 mL). The solution was stirred for 3 h and then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ and concentrated in vacuo; this procedure was repeated. A portion (0.22 mmol) of the product amine was dissolved in CH₂Cl₂ (4 mL). The resultant solution was charged sequentially with N, N-diisopropylethylamine (0.16 mL, 0.88 mmol) and (meta-trifluoromethyl-phenyl)isocyanate (0.033 mL, 0.22 mmol). The reaction was stirred for 12 h and partitioned between EtOAc and sat. NH₄Cl. The organic phase was washed with sat. NaHCO₃ and brine, and then dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was dissolved in MeOH (6 mL). The resultant solution was charged with 5% Pd/C, Degussa style (50 mg), stirred under H₂ (1 atm) for 12 h at RT, filtered, and concentrated in vacuo. The residue was purified by reverse-phase HPLC to afford the title compound as a white powder after lyophilization. MS found: (M + H)⁺ = 521.5.

20

Example 3

{2-[(3S)-1-{(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl}-2-oxo-pyrrolidin-3-ylcarbamoyl]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester

25

(3a) A solution of {(3S)-1-[(1S, 2S)-1-(benzyloxycarbonylamino-methyl)-2-hydroxy-pent-3-ynyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (0.097 mg, 0.22 mmol, see procedure 1b above) was dissolved in CH₂Cl₂ (4 mL) and treated with TFA (2 mL). The solution was stirred for 3 h and then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ and

concentrated in vacuo; this procedure was repeated. The product amine was dissolved in 1:1 DMF/CH₂Cl₂ (4 mL). The resultant solution was charged sequentially with N, N-diisopropylethylamine (0.16 mL, 0.88 mmol), N-Boc-2-amino-5-(trifluoromethyl)-benzoic acid (S. Takagishi, et al., *Synlett* 1992, 360; 73 mg, 0.24 mmol), and HATU (97 mg, 0.26 mmol). The reaction was stirred for 12 h and partitioned between EtOAc and sat. NH₄Cl. The organic phase was washed with sat. NaHCO₃ and brine, and then dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by flash chromatography afforded (2-{(3S)-1-[(1S, 2S)-1-(benzyloxycarbonylamino-methyl)-2-hydroxypent-3-ynyl]-2-oxo-pyrrolidin-3-ylcarbamoyl}-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (87 mg, 64% yield). MS found: (M + Na)⁺ = 655.5.

(3b) The compound (2-{(3S)-1-[(1S, 2S)-1-(benzyloxycarbonylamino-methyl)-2-hydroxypent-3-ynyl]-2-oxo-pyrrolidin-3-ylcarbamoyl}-4-trifluoromethyl-phenyl)-carbamic acid tert-butyl ester (87 mg, 0.14 mmol) was dissolved in MeOH (4 mL). The resultant solution was charged with 5% Pd/C, Degussa style (10 mg), stirred under H₂ (1 atm) for 12 h at RT, filtered, and concentrated in vacuo. The residue was redissolved in MeOH (4 mL). The resultant solution was charged sequentially with 2,4-dimethylbenzaldehyde (0.015 mL, 0.11 mmol) and sodium cyanoborohydride (10 mg), stirred for 12 h at RT, quenched with sat. NaHCO₃, and extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by reverse-phase

HPLC afforded the title compound as a white powder after lyophilization (15 mg). MS found: $(M + H)^+ = 621.5$.

Example 4

5 2-Amino-N-[(3S)-1-[(1S, 2S)-1-[(2,4-dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-yl]-5-trifluoromethyl-benzamide

(4a) The compound {2-[(3S)-1-[(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-ylcarbamoyl]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester (9 mg) was dissolved in 3 mL of 2:1 CH₂Cl₂/TFA. The resultant solution was stirred for 3 h and then concentrated in vacuo. The residue was dissolved in 15 TFA and concentrated in vacuo; this procedure was repeated. Lyophilization (H₂O/MeCN) afforded the title compound as a white powder (5 mg). MS found: $(M + H)^+ = 521.5$.

20

Example 5

3-Amino-N-[(3S)-1-[(1S, 2S)-1-[(2,4-dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-yl]-5-trifluoromethyl-benzamide

25 (5a) The procedure 3a was repeated on a modified scale, substituting 3-nitro-5-trifluoromethylbenzoic acid (53 mg, 0.227 mmol) for N-Boc-2-amino-5-(trifluoromethyl)-benzoic acid. The purified product was then carried through procedure 3b to afford the title compound as a 30 white powder after reverse-phase HPLC and lyophilization. MS found: $(M + H)^+ = 521.4$.

Example 6

2-Amino-N-{(3S)-1-[(1S)-1-tert-butylcarbamoyl-2-(2,4-dimethyl-benzylamino)-ethyl]-2-oxo-pyrrolidin-3-yl}-5-trifluoromethyl-benzamide

5 (6a) The procedures 1a - 1b (see above) were followed on a modified scale, substituting (2-tert-butoxycarbonylamino-2-tert-butylcarbamoyl-ethyl)-carbamic acid benzyl ester, to afford {(3S)-1-[(1S)-2-benzyloxycarbonylamino-1-tert-butylcarbamoyl-ethyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (~40%
10 yield). MS found: $(M + Na)^+ = 499.9$.

(6b) The compound {(3S)-1-[(1S)-2-benzyloxycarbonylamino-1-tert-butylcarbamoyl-ethyl]-2-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (250 mg, 0.5 mmol) was
15 carried through procedures 3a, 3b, and 4a (see above) to afford the title compound as a white powder after reverse-phase HPLC and lyophilization. MS found: $(M + H)^+ = 548.4$.

20

Table of Examples

The following table illustrates examples of the present invention. The data in the "MS" columns represent the values observed for the (M + H)⁺ ions in electrospray mass spectroscopy experiments. The substituents listed in each table are to be paired with the structure embedded in the table heading. The synthesis of all of these compounds has been described in detail in the previous section (Examples).

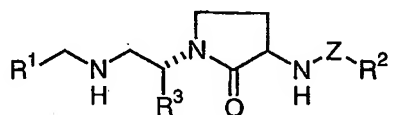
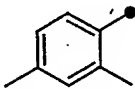
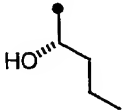
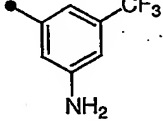
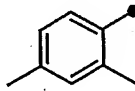
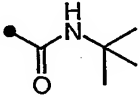
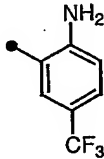


Table 1: examples 1 - 6

No.	R ¹	R ³	*	Z	R ²	MS
1			S	-C(O)-		506
2			S	-CONH-		521
3			S	-C(O)-		621
4			S	-C(O)-		521

5			<i>S</i>	-C(O)-		521
6			<i>S</i>	-C(O)-		548

UTILITY

Compounds of formula I are shown to be modulators of chemokine and chemokine receptor activity using assays known by those skilled in the art. In this section, we describe these assays and give their literature reference. By displaying activity in these assays of MCP-1 antagonism, compounds of formula I are expected to be useful in the treatment of human diseases associated with chemokines and their cognate receptors.

10

Antagonism of MCP-1 Binding to Human PBMC

(Yoshimura et al., *J. Immunol.* 1990, 145, 292)

All examples of the present invention have activity in the antagonism of MCP-1 binding to human PBMC (human peripheral blood mononuclear cells) described here. The definition of activity in this assay is a compound demonstrating 50% inhibition of MCP-1 binding (IC_{50}) at a concentration of 20 μM or lower.

Millipore filter plates (#MABVN1250) are treated with 100 μl of binding buffer (0.5% bovine serum albumin, 20 mM HEPES buffer and 5 mM magnesium chloride in RPMI 1640 media) for thirty minutes at room temperature. To measure binding, 50 μl of binding buffer, with or without a known concentration compound, is combined with 50 μl of 125 -I labeled human MCP-1 (to give a final concentration of 150 pM radioligand) and 50 μl of binding buffer containing 5×10^5 cells. Cells used for such binding assays can include human peripheral blood mononuclear cells isolated by Ficoll-Hypaque gradient centrifugation, human monocytes (Weiner et al., *J. Immunol. Methods.* 1980, 36, 89), or the THP-1 cell line which expresses the endogenous receptor. The mixture of compound, cells and

30

radioligand are incubated at room temperature for thirty minutes. Plates are placed onto a vacuum manifold, vacuum applied, and the plates washed three times with binding buffer containing 0.5M NaCl. The plastic skirt
5 is removed from the plate, the plate allowed to air dry, the wells punched out and counted. The percent inhibition of binding is calculated using the total counts obtained in the absence of any competing compound and the background binding determined by addition of 100
10 nM MCP-1 in place of the test compound.

Antagonism of MCP-1-induced Calcium Influx

(Sullivan, et al. *Methods Mol. Biol.* 1999, 114, 125-133)

Calcium mobilization is measured using the
15 fluorescent Ca^{2+} indicator dye, Fluo-3. Cells are incubated at 8×10^5 cells/ml in phosphate-buffered saline containing 0.1% bovine serum albumin, 20 mM HEPES buffer, 5 mM glucose, 1% fetal bovine serum, 4 μM Fluo-3 AM and 2.5 mM probenecid for 60 minutes at 37°C. Cells
20 used for such calcium assays can include human monocytes (Weiner et al., *J. Immunol. Methods.* 1980, 36, 89) or cell lines which express the endogenous CCR2 receptor, such as THP-1 and MonoMac-6. The cells are then washed three times in phosphate-buffered saline containing 0.1%
25 bovine serum albumin, 20 mM HEPES, 5 mM glucose and 2.5 mM probenecid. The cells are resuspended in phosphate-buffered saline containing 0.5% bovine serum albumin, 20 mM HEPES and 2.5 mM probenecid at a final concentration of $2-4 \times 10^6$ cells/ml. Cells are plated into 96-well,
30 black-wall microplates (100 μl /well) and the plates centrifuged at 200 x g for 5 minutes. Various concentrations of compound are added to the wells (50

μl/well) and after 5 minutes, 50 μl/well of MCP-1 is added to give a final concentration of 10 nM. Calcium mobilization is detected by using a fluorescent-imaging plate reader. The cell monolayer is excited with an argon laser (488 nm) and cell-associated fluorescence measured for 3 minutes, (every second for the first 90 seconds and every 10 seconds for the next 90 seconds). Data are generated as arbitrary fluorescence units and the change in fluorescence for each well determined as the maximum-minimum differential. Compound-dependent inhibition is calculated relative to the response of MCP-1 alone.

Antagonism of MCP-1-induced Human PBMC Chemotaxis

(Bacon et al., *Brit. J. Pharmacol.* 1988, 95, 966)

Neuroprobe MBA96-96-well chemotaxis chamber, Polyfiltronics MPC 96 well plate, and Neuroprobe polyvinylpyrrolidone-free polycarbonate PFD5 8-micron filters are warmed in a 37 °C incubator. Human Peripheral Blood Mononuclear Cells (PBMCs) (Boyum et al., *Scand. J. Clin. Lab Invest. Suppl.* 1968, 97, 31), freshly isolated via the standard ficoll density separation method, are suspended in DMEM at 1×10^7 c/ml and warmed at 37 °C. A 60nM solution of human MCP-1 is also warmed at 37 °C.

Dilutions of test compounds are made up at 2x the concentration needed in DMEM. The PBMC suspension and the 60nm MCP-1 solution are mixed 1:1 in polypropylene tubes with prewarmed DMEM with or without a dilution of the test compounds. These mixtures are warmed in a 37 °C tube warmer. In order to initiate the assay, the MCP-1/compound mixture (400 μL) is added into the wells of the Polyfiltronics MPC 96 well plate that has been placed into the bottom part of the Neuroprobe chemotaxis

chamber. The 8 micron filter is placed on top of the 96 well plate, a rubber gasket is attached to the bottom of the upper chamber, and the chamber is assembled. The cell suspension/compound mixture (200 μ l) is added to the appropriate wells of the upper chamber. The upper chamber is covered with a plate sealer, and the assembled unit is placed in a 37 °C incubator for 45 min. After incubation, the plate sealer is removed and all the remaining cell suspension is aspirated off. The chamber is disassembled and the filter is removed. The unmigrated cells are washed away using a gentle stream of phosphate buffered saline, and the top of the filter is wiped with the tip of a rubber squeegee. This wash is repeated twice more. The filter is air dried and then immersed completely in Wright Geimsa stain for 45 sec. The filter is washed by soaking in distilled water for 7 min, and the filter is soaked again for 15 sec in fresh distilled water. The filter is air dried. Migrated cells on the filter are quantified by visual microscopy.

20

Mammalian chemokine receptors provide a target for interfering with or promoting immune cell function in a mammal, such as a human. Compounds that inhibit or promote chemokine receptor function are particularly useful for modulating immune cell function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory, infectious, and immunoregulatory disorders and diseases, including asthma and allergic diseases, infection by pathogenic microbes (which, by definition, includes viruses), as well as autoimmune pathologies such as the rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation or
5 infectious disease. As a result, one or more inflammatory process, such as leukocyte migration, adhesion, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited.

10 In addition, an instant compound that promotes internalization/desensitization of a mammalian chemokine receptor without also inducing its primary function may be administered to inhibit (i.e., reduce or prevent) disease. If one contemplates the delivery of sufficient
15 compound to cause the loss of receptor expression on cells through the induction of chemokine receptor internalization, than one can imagine that such a compound would also be useful for the treatment of the aforementioned inflammatory, allergic and autoimmune
20 diseases.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals, including but not limited to, cows, sheep, goats, horses,
25 dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species. The subject treated in the methods above is a mammal, male or female,
30 in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, partial antagonism and/or partial agonism.

Diseases or conditions of human or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic cellulitis (e.g., Wells's syndrome), eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), eosinophilic fasciitis (e.g., Shulman's syndrome), delayed-type hypersensitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), eosinophilia-myalgia syndrome due to the ingestion of contaminated tryptophan, insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinophilic myositis, eosinophilic fasciitis; cancers

with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, 5 certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis. Infectious diseases or conditions of human or other species which can be treated with inhibitors of chemokine receptor function, include, 10 but are not limited to, HIV. The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory, infectious and immunoregulatory disorders and diseases.

15 In addition, treatment of the aforementioned inflammatory, allergic and autoimmune diseases can also be contemplated for compounds that promote chemokine receptor internalization without stimulating chemokine receptor function, particularly if one contemplates the 20 delivery of sufficient compound to cause the loss of receptor expression on cells.

In another aspect, the instant invention may be used to evaluate the putative specific agonists or antagonists of a G protein coupled receptor. The present invention 25 is directed to the use of these compounds in the preparation and execution of screening assays for compounds that modulate the activity of chemokine receptors. Furthermore, the compounds of this invention are useful in establishing or determining the binding 30 site of other compounds to chemokine receptors, e.g., by competitive inhibition or as a reference in an assay to compare its known activity to a compound with an unknown activity. When developing new assays or protocols,

compounds according to the present invention could be used to test their effectiveness. Specifically, such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving the
5 aforementioned diseases. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors. In addition, one could utilize compounds of this invention to examine the specificity of G protein coupled receptors
10 that are not thought to be chemokine receptors, either by serving as examples of compounds which do not bind or as structural variants of compounds active on these receptors which may help define specific sites of interaction.

15 The compounds of the present invention are used to treat or prevent disorders selected from rheumatoid arthritis, osteoarthritis, septic shock, atherosclerosis, aneurism, fever, cardiovascular effects, haemodynamic shock, sepsis syndrom, post ischemic reperfusion injury,
20 malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, autoimmune diseases, skin inflammatory diseases, multiple sclerosis, radiation damage, hyperoxic
25 alveolar injury, HIV, HIV dementia, non-insulin dependent diabetes melitus, asthma, allergic rhinitis, atopic dermatitis, idiopathic pulmonary fibrosis, bullous pemphigoid, helminthic parasitic infections, allergic colitis, eczema, conjunctivitis, transplantation,
30 familial eosinophilia, eosinophilic cellulitis, eosinophilic pneumonias, eosinophilic fasciitis, eosinophilic gastroenteritis, drug induced eosinophilia, cystic fibrosis, Churg-Strauss syndrome, lymphoma,

Hodgkin's disease, colonic carcinoma, Felty's syndrome, sarcoidosis, uveitis, Alzheimer, Glomerulonephritis, and systemic lupus erythematosus.

Furthermore, the compounds are used to treat or
5 prevent inflammatory disorders selected from
osteoarthritis, aneurism, fever, cardiovascular effects,
Crohn's disease, congestive heart failure, autoimmune
diseases, HIV-infection, HIV-associated dementia,
psoriasis, idiopathic pulmonary fibrosis, transplant
10 arteriosclerosis, physically- or chemically-induced brain
trauma, inflammatory bowel disease, alveolitis, colitis,
systemic lupus erythematosus, nephrotoxic serum
nephritis, glomerularnephritis, asthma, multiple
sclerosis, arteriosclerosis, and rheumatoid arthritis.

15 In another aspect of the invention, the compounds
are used to treat or prevent inflammatory disorders
selected from rheumatoid arthritis, atherosclerosis, and
multiple sclerosis.

Combined therapy to prevent and treat inflammatory,
20 infectious and immunoregulatory disorders and diseases,
including asthma and allergic diseases, as well as
autoimmune pathologies such as rheumatoid arthritis and
atherosclerosis, and those pathologies noted above is
illustrated by the combination of the compounds of this
25 invention and other compounds which are known for such
utilities. For example, in the treatment or prevention
of inflammation, the present compounds may be used in
conjunction with an anti-inflammatory or analgesic agent
such as an opiate agonist, a lipxygenase inhibitor, a
30 cyclooxygenase-2 inhibitor, an interleukin inhibitor,
such as an interleukin-1 inhibitor, a tumor necrosis
factor inhibitor, an NMDA antagonist, an inhibitor or
nitric oxide or an inhibitor of the synthesis of nitric

oxide, a non-steroidal anti-inflammatory agent, a phosphodiesterase inhibitor, or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, interferon alpha and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H₂-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levodesoxy-ephedrine; and antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compound of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) integrin antagonists such as those for selectins, ICAMs and VLA-4; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine, pyrileamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as b2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuteral, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-102,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acetaminophen, alclofenac, clidananac, diclofenac,

fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, 5 mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, 10 bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (I) other antagonists of the chemokine receptors; (j) cholesterol lowering agents such as HMG-CoA reductase 15 inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotonic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; 20 (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferons (interferon alpha-2a, interferon-2B, interferon alpha-N3, interferon beta-1a, 25 interferon beta-1b, interferon gamma-1b); (m) antiviral compounds such as efavirenz, nevirapine, indinavir, ganciclovir, lamivudine, famciclovir, and zalcitabine; (o) other compound such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine 30 and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. The weight ratio of the compound of the present invention to the second active

ingredient may be varied and will depend upon the effective doses of each ingredient.

Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is also meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the

chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known
5 factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment;
10 the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of
15 the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg
20 of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or
25 the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal
30 skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with
5 respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be
10 combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the
15 oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be
20 incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and
25 the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum,
30 and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar

vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any

unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules

- 5 containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active
10 ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

15 Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with
20 sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl
25 cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound
30 of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10

milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the

formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of

5 hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

10 These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to

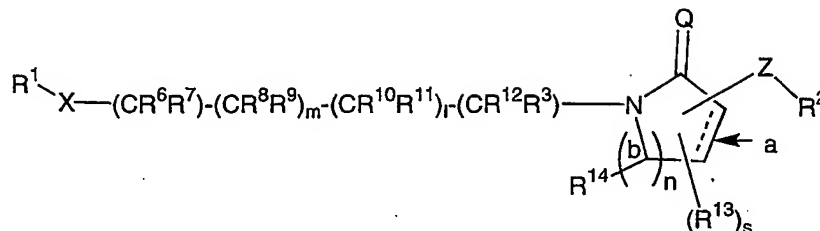
15 those skilled in the art, once armed with the present disclosure.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within

20 the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

What is claimed is:

1. A compound of Formula (I)



(I)

or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

- 10 Z is selected from a bond, -NR¹⁸C(O)-, -NR¹⁸C(S)-, -NR¹⁸C(O)NH-, -NR¹⁸C(S)NH-, -NR¹⁸SO₂-, -NR¹⁸SO₂NH-, -C(O)NR¹⁸-, -OC(O)NR¹⁸-, -NR¹⁸C(O)O-, -(CR²⁵R²⁵)ₜ-, -CR²⁴=CR²⁴-, -CR²⁵R²⁵C(O)-, -C(O)CR²⁵R²⁵-, -CR²⁵R²⁵C(=N-OR²⁶)-, -O-CR²⁴R²⁴-, -C R²⁴R²⁴-O-, -O-,
 15 -NR¹⁹-, -NR¹⁹-CR²⁴R²⁴-, -CHR²⁴-NR¹⁹-, -S(O)ₚ-, -S(O)ₚ-CR²⁴R²⁴-, and -S(O)ₚ-NR¹⁹-;

Q is selected from O or S;

- 20 wherein neither Z nor R¹³ are connected to a carbon atom labeled (b);

X is selected from -NR¹⁷- and -CHR¹⁶NR¹⁷-;

- 25 bond (a) is a single or double bond;

alternatively, when n is equal to 2, two atoms labeled (b) may join through a double bond;

- 30 R¹ is selected from a C₆-₁₀ aryl group substituted with 0-5 R⁴ and a 5-10 membered heteroaryl system

containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁴;

5 R² is selected from a C₆₋₁₀ aryl group substituted with 0-5 R⁵ and a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R⁵;

10 R³ is selected from H, (CRR)_qOH, (CRR)_qSH, (CRR)_qOR^{3d}, (CRR)_qS(O)_pR^{3d}, (CRR)_rC(O)R^{3b}, (CRR)_qNR^{3a}R^{3a}, (CRR)_rC(O)NR^{3a}R^{3a}, (CRR)_rC(O)NR^{3a}OR^{3d}, (CRR)_qSO₂NR^{3a}R^{3a}, (CRR)_rC(O)OR^{3d}, a (CRR)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{3e}, and a (CRR)_r-5-10 membered heterocyclic system containing 15 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3e};

with the proviso that R³ is not H if R⁶ is H;

20 alternatively, R³ and R¹² join to form a C₃₋₆ cycloalkyl substituted with 0-2 R^{3g}, a 5-6 membered lactam ring in which carbon atoms of the ring are substituted with 0-2 R^{3g}, or a 5-6 membered lactone ring in which carbon atoms of the ring are substituted with 25 0-2 R^{3g};

R^{3a}, at each occurrence, is independently selected from H, methyl substituted with 0-1 R^{3c}, C₂₋₆ alkyl substituted with 0-3 R^{3e}, C₃₋₈ alkenyl substituted with 0-3 R^{3e}, C₃₋₈ alkynyl substituted with 0-3 R^{3e}, 30 (CH₂)_rC₃₋₆ cycloalkyl, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{3e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4

heteroatoms selected from N, O, and S, substituted with 0-3 R^{3e};

5 R^{3b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-3 R^{3e}, C₂₋₈ alkenyl substituted with 0-3 R^{3e}, C₂₋₈ alkynyl substituted with 0-3 R^{3e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{3e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms
10 selected from N, O, and S, substituted with 0-3 R^{3e};

R^{3c} is independently selected from -C(O)R^{3b}, -C(O)OR^{3d}, -C(O)NR^{3f}R^{3f}, and (CH₂)_rphenyl;

15 R^{3d}, at each occurrence, is independently selected from H, methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{3e}, C₃₋₆ alkenyl substituted with 0-3 R^{3e}, C₃₋₆ alkynyl substituted with 0-3 R^{3e}, a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{3e}, and a (CH₂)_r-5-6 membered
20 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3e};

R^{3e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
25 (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{3f}R^{3f}, and (CH₂)_rphenyl;

R^{3f}, at each occurrence, is selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

30

- R^{3g} is selected from $(CHR)_rOH$, $(CHR)_rSH$, $(CHR)_rOR^{3d}$,
 $(CHR)_rS(O)_rR^{3d}$, $(CHR)_rC(O)R^{3b}$, $(CHR)_rNR^{3a}R^{3a}$,
 $(CHR)_rC(O)NR^{3a}R^{3a}$, $(CHR)_rC(O)NR^{3a}OR^{3d}$,
 $(CHR)_rSO_2NR^{3a}R^{3a}$, $(CHR)_rC(O)OR^{3d}$, and a $(CHR)_r-C_{3-10}$
 5 carbocyclic residue substituted with 0-5 R^{3e} ;
- R , at each occurrence, is independently selected from H,
 C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$
 cycloalkyl, $(CHR)_rC(O)NR^{3a}R^{3a}$, and $(CHR)_rC(O)OR^{3d}$, and
 10 $(CH_2)_r$ phenyl substituted with 0-3 R^{3e} , and a
 $(CH_2)_r-5-10$ membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-3 R^{3e} ;
- 15 R^4 , at each occurrence, is selected from C_{1-8} alkyl, C_{2-8}
 alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, Cl, Br,
 I, F, NO_2 , CN, $(CR'R')_rNR^{4a}R^{4a}$, $(CR'R')_rOH$,
 $(CR'R')_rO(CR'R')_rR^{4d}$, $(CR'R')_rSH$, $(CR'R')_rC(O)H$,
 $(CR'R')_rS(CR'R')_rR^{4d}$, $(CR'R')_rC(O)OH$,
 20 $(CR'R')_rC(O)(CR'R')_rR^{4b}$, $(CR'R')_rC(O)NR^{4a}R^{4a}$,
 $(CR'R')_rNR^{4f}C(O)(CR'R')_rR^{4b}$, $(CR'R')_rC(O)O(CR'R')_rR^{4d}$,
 $(CR'R')_rOC(O)(CR'R')_rR^{4b}$,
 $(CR'R')_rNR^{4f}C(O)O(CR'R')_rR^{4d}$, $(CR'R')_rOC(O)NR^{4a}R^{4a}$,
 $(CR'R')_rNR^{4a}C(S)NR^{4a}(CR'R')_rR^{4d}$,
 25 $(CR'R')_rNR^{4a}C(O)NR^{4a}R^{4a}$, $(CR'R')_rC(=NR^{4f})NR^{4a}R^{4a}$,
 $(CR'R')_rNHC(=NR^{4f})NR^{4f}R^{4f}$, $(CR'R')_rS(O)_p(CR'R')_rR^{4b}$,
 $(CR'R')_rS(O)_2NR^{4a}R^{4a}$, $(CR'R')_rNR^{4f}S(O)_2NR^{4a}R^{4a}$,
 $(CR'R')_rNR^{4f}S(O)_2(CR'R')_rR^{4b}$, C_{1-6} haloalkyl, C_{2-8}
 alkenyl substituted with 0-3 R' , C_{2-8} alkynyl
 30 substituted with 0-3 R' , and $(CR'R')_r$ phenyl
 substituted with 0-3 R^{4e} ;

alternatively, two R⁴ on adjacent atoms on R¹ may join to form a cyclic acetal;

5 R^{4a}, at each occurrence, is independently selected from H, methyl substituted with 0-1R^{4g}, C₂₋₆ alkyl substituted with 0-2 R^{4e}, C₃₋₈ alkenyl substituted with 0-2 R^{4e}, C₃₋₈ alkynyl substituted with 0-2 R^{4e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{4e}, and a (CH₂)_r-5-10 membered heterocyclic
10 system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e};

R^{4b}, at each occurrence, is selected from C₁₋₆ alkyl substituted with 0-2 R^{4e}, C₃₋₈ alkenyl substituted with 0-2 R^{4e}, C₃₋₈ alkynyl substituted with 0-2 R^{4e},
15 a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-3 R^{4e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{4e};

20 R^{4d}, at each occurrence, is selected from C₃₋₈ alkenyl substituted with 0-2 R^{4e}, C₃₋₈ alkynyl substituted with 0-2 R^{4e}, methyl, CF₃, C₂₋₆ alkyl substituted with 0-3 R^{4e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{4e}, and a (CH₂)_r-5-6 membered
25 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{4e};

R^{4e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_r-C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_r-CF₃, (CH₂)_r-OC₁₋₅ alkyl, OH, SH, (CH₂)_r-SC₁₋₅ alkyl, (CH₂)_r-NR^{4f}R^{4f}, and (CH₂)_r-phenyl;
30

R^{4f} , at each occurrence, is selected from H, C_{1-5} alkyl, and C_{3-6} cycloalkyl, and phenyl;

R^{4g} is independently selected from $-C(O)R^{4b}$, $-C(O)OR^{4d}$,
5 $-C(O)NR^{4f}R^{4f}$, and $(CH_2)_r$ phenyl;

R^5 , at each occurrence, is selected from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, Cl, Br, I, F, NO_2 , CN, $(CR'R')_rNR^{5a}R^{5a}$, $(CR'R')_rOH$,
10 $(CR'R')_rO(CR'R')_rR^{5d}$, $(CR'R')_rSH$, $(CR'R')_rC(O)H$,
 $(CR'R')_rS(CR'R')_rR^{5d}$, $(CR'R')_rC(O)OH$,
 $(CR'R')_rC(O)(CR'R')_rR^{5b}$, $(CR'R')_rC(O)NR^{5a}R^{5a}$,
 $(CR'R')_rNR^{5f}C(O)(CR'R')_rR^{5b}$, $(CR'R')_rC(O)O(CR'R')_rR^{5d}$,
 $(CR'R')_rOC(O)(CR'R')_rR^{5b}$, $(CR'R')_rNR^{5f}C(O)O(CR'R')_rR^{5d}$,
15 $(CR'R')_rOC(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{5a}C(O)NR^{5a}R^{5a}$,
 $(CR'R')_rC(=NR^{5f})NR^{5a}R^{5a}$, $(CR'R')_rNHC(=NR^{5f})NR^{5f}R^{5f}$,
 $(CR'R')_rS(O)_p(CR'R')_rR^{5b}$, $(CR'R')_rS(O)_2NR^{5a}R^{5a}$,
 $(CR'R')_rNR^{5a}S(O)_2NR^{5a}R^{5a}$, $(CR'R')_rNR^{5f}S(O)_2(CR'R')_rR^{5b}$,
 C_{1-6} haloalkyl, C_{2-8} alkenyl substituted with 0-3 R' ,
20 C_{2-8} alkynyl substituted with 0-3 R' , $(CR'R')_r$ phenyl substituted with 0-3 R^{5e} , and a $(CRR)_r$ -5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5c} ;

25 alternatively, two R^5 on adjacent atoms on R^2 may join to form a cyclic acetal;

R^{5a} , at each occurrence, is independently selected from H, methyl substituted with 0-1 R^{5g} , C_{2-6} alkyl
30 substituted with 0-2 R^{5e} , C_{3-8} alkenyl substituted with 0-2 R^{5e} , C_{3-8} alkynyl substituted with 0-2 R^{5e} , a $(CH_2)_r$ - C_{3-10} carbocyclic residue substituted with

0-5 R^{5e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5e};

5 R^{5b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-2 R^{5e}, C₃₋₈ alkenyl substituted with 0-2 R^{5e}, C₃₋₈ alkynyl substituted with 0-2 R^{5e}, a (CH₂)_rC₃₋₆ carbocyclic residue substituted with 0-3 R^{5e}, and a (CH₂)_r-5-6 membered
10 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5e};

R^{5d}, at each occurrence, is independently selected from C₃₋₈ alkenyl substituted with 0-2 R^{5e}, C₃₋₈ alkynyl
15 substituted with 0-2 R^{5e}, methyl, CF₃, C₂₋₆ alkyl substituted with 0-3 R^{5e}, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{5e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted
20 with 0-3 R^{5e};

R^{5e}, at each occurrence, is selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, SH,
25 (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{5f}R^{5f}, and (CH₂)_rphenyl;

R^{5f}, at each occurrence, is selected from H, C₁₋₅ alkyl, and C₃₋₆ cycloalkyl, and phenyl;

30 R^{5g} is independently selected from -C(O)R^{5b}, -C(O)OR^{5d}, -C(O)NR^{5f}R^{5f}, and (CH₂)_rphenyl;

R', at each occurrence, is selected from H, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, (CH₂)_rC₃₋₆ cycloalkyl, and (CH₂)_rphenyl substituted with R^{5e};

5 R⁶, is selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, (CRR)_qOH, (CRR)_qSH, (CRR)_qOR^{6d}, (CRR)_qS(O)_pR^{6d}, (CRR)_rC(O)R^{6b}, (CRR)_rNR^{6a}R^{6a}, (CRR)_rC(O)NR^{6a}R^{6a}, (CRR)_rC(O)NR^{6a}OR^{6d}, (CRR)SO₂NR^{6a}R^{6a}, (CRR)_rC(O)OR^{6d}, a (CRR)_r-C₃₋₁₀ carbocyclic residue
 10 substituted with 0-5 R^{6e}, and a (CRR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e};

alternatively, R⁶ and R⁷ join to form a C₃₋₆ cycloalkyl
 15 substituted with 0-2 R^{6g}, a 5-6 membered ring lactam substituted with 0-2 R^{6g}, or a 5-6 membered ring lactone substituted with 0-2 R^{6g};

R^{6a}, at each occurrence, is independently selected from H,
 20 methyl, C₂₋₆ alkyl substituted with 0-3 R^{6e}, C₃₋₈ alkenyl substituted with 0-3 R^{6e}, C₃₋₈ alkynyl substituted with 0-3 R^{6e}, (CH₂)_rC₃₋₆ cycloalkyl, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{6e}, and a (CH₂)_r-5-10 membered heterocyclic system
 25 containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e};

R^{6b}, at each occurrence, is independently selected from
 C₁₋₆ alkyl substituted with 0-3 R^{6e}, C₂₋₈ alkenyl
 30 substituted with 0-3 R^{6e}, C₂₋₈ alkynyl substituted with 0-3 R^{6e}, a (CH₂)_r-C₃₋₆ carbocyclic residue

substituted with 0-2 R^{6e} , and a $(CH_2)_r$ -5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e} ;

5 R^{6d} , at each occurrence, is independently selected from H, methyl, $-CF_3$, C_{2-6} alkyl substituted with 0-3 R^{6e} , C_{3-6} alkenyl substituted with 0-3 R^{6e} , C_{3-6} alkynyl substituted with 0-3 R^{6e} , a C_{3-10} carbocyclic residue substituted with 0-3 R^{6e} , and a $(CH_2)_r$ -5-6 membered
 10 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{6e} ;

R^{6e} , at each occurrence, is independently selected from C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-6}
 15 cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, $-O-C_{1-6}$ alkyl, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{6f}R^{6f}$, and $(CH_2)_r$ phenyl;

R^{6f} , at each occurrence, is independently selected from H,
 20 C_{1-6} alkyl, and C_{3-6} cycloalkyl;

R^{6g} is selected from $(CHR)_qOH$, $(CHR)_qSH$, $(CHR)_qOR^{6d}$,
 $(CHR)_qS(O)_pR^{6d}$, $(CHR)_rC(O)R^{6b}$, $(CHR)_qNR^{6a}R^{6a}$,
 $(CHR)_rC(O)NR^{6a}R^{6a}$, $(CHR)_rC(O)NR^{6a}OR^{6d}$,
 25 $(CHR)_qSO_2NR^{6a}R^{6a}$, $(CHR)_rC(O)OR^{6d}$, and a $(CHR)_r$ - C_{3-10} carbocyclic residue substituted with 0-5 R^{6e} ;

R^7 , is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CRR)_qOH$, $(CRR)_qSH$, $(CRR)_qOR^{7d}$,
 30 $(CRR)_qS(O)_pR^{7d}$, $(CRR)_rC(O)R^{7b}$, $(CRR)_rNR^{7a}R^{7a}$,

(CRR)_rC(O)NR^{7a}R^{7a}, (CRR)_rC(O)NR^{7a}OR^{7d},
(CRR)_qSO₂NR^{7a}R^{7a}, (CRR)_rC(O)OR^{7d}, a (CRR)_r-C₃₋₁₀
carbocyclic residue substituted with 0-5 R^{7e}, and a
(CRR)_r-5-10 membered heterocyclic system containing
5 1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{7e};

R^{7a}, at each occurrence, is independently selected from H,
methyl, C₂₋₆ alkyl substituted with 0-3 R^{7e}, C₃₋₈
10 alkenyl substituted with 0-3 R^{7e}, C₃₋₈ alkynyl
substituted with 0-3 R^{7e}, (CH₂)_rC₃₋₆ cycloalkyl, a
(CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5
R^{7e}, and a (CH₂)_r-5-10 membered heterocyclic system
containing 1-4 heteroatoms selected from N, O, and
15 S, substituted with 0-3 R^{7e};

R^{7b}, at each occurrence, is independently selected from
C₁₋₆ alkyl substituted with 0-3 R^{7e}, C₂₋₈ alkenyl
substituted with 0-3 R^{7e}, C₂₋₈ alkynyl substituted
20 with 0-3 R^{7e}, a (CH₂)_r-C₃₋₆ carbocyclic residue
substituted with 0-2 R^{7e}, and a (CH₂)_r-5-6 membered
heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{7e};

25 R^{7d}, at each occurrence, is independently selected from H,
methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{7e},
C₃₋₆ alkenyl substituted with 0-3 R^{7e}, C₃₋₆ alkynyl
substituted with 0-3 R^{7e}, a C₃₋₁₀ carbocyclic residue
substituted with 0-3 R^{7e}, and a (CH₂)_r-5-6 membered

heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{7e};

5 R^{7e}, at each occurrence, is independently selected from
C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆
cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃,
(CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅
alkyl, (CH₂)_rNR^{7f}R^{7f}, and (CH₂)_rphenyl;

10 R^{7f}, at each occurrence, is independently selected from H,
C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

R⁸ is selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
alkynyl, (CRR)_rOH, (CRR)_rSH, (CRR)_rOR^{8d},
15 (CRR)_rS(O)_pR^{8d}, (CRR)_rC(O)R^{8b}, (CRR)_rNR^{8a}R^{8a},
(CRR)_rC(O)NR^{8a}R^{8a}, (CRR)_rC(O)NR^{8a}OR^{8d},
(CRR)_rSO₂NR^{8a}R^{8a}, (CRR)_rC(O)OR^{8d}, a (CRR)_r-C₃₋₁₀
carbocyclic residue substituted with 0-5 R^{8e}, and a
(CRR)_r-5-10 membered heterocyclic system containing
20 1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{8e};

alternatively, R⁸ and R⁹ join to form a C₃₋₆ cycloalkyl
substituted with 0-2 R^{8g}, a 5-6 membered ring lactam
25 substituted with 0-2 R^{8g}, or a 5-6 membered ring
lactone substituted with 0-2 R^{8g};

R^{8a}, at each occurrence, is independently selected from H,
methyl, C₂₋₆ alkyl substituted with 0-3 R^{8e}, C₃₋₈
30 alkenyl substituted with 0-3 R^{8e}, C₃₋₈ alkynyl
substituted with 0-3 R^{8e}, (CH₂)_rC₃₋₆ cycloalkyl, a

(CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{8e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{8e};

5

R^{8b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-3 R^{8e}, C₂₋₈ alkenyl substituted with 0-3 R^{8e}, C₂₋₈ alkynyl substituted with 0-3 R^{8e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{8e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{8e};

10

R^{8d}, at each occurrence, is independently selected from H, methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{8e}, C₃₋₆ alkenyl substituted with 0-3 R^{8e}, C₃₋₆ alkynyl substituted with 0-3 R^{8e}, a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{8e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{8e};

15

20

R^{8e}, at each occurrence, is independently selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃, (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{8f}R^{8f}, and (CH₂)_rphenyl;

25

R^{8f}, at each occurrence, is independently selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

30

R^{8g} is selected from $(CHR)_qOH$, $(CHR)_qSH$, $(CHR)_qOR^{8d}$,
 $(CHR)_qS(O)_pR^{8d}$, $(CHR)_rC(O)R^{8b}$, $(CHR)_qNR^{8a}R^{8a}$,
 $(CHR)_rC(O)NR^{8a}R^{8a}$, $(CHR)_rC(O)NR^{8a}OR^{8d}$,
 $(CHR)_qSO_2NR^{8a}R^{8a}$, $(CHR)_rC(O)OR^{8d}$, and a $(CHR)_r-C_{3-10}$
 5 carbocyclic residue substituted with 0-5 R^{8e} ;

R^9 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}
 alkynyl, $(CRR)_rOH$, $(CRR)_rSH$, $(CRR)_rOR^{9d}$,
 $(CRR)_rS(O)_pR^{9d}$, $(CRR)_rC(O)R^{9b}$, $(CRR)_rNR^{9a}R^{9a}$,
 10 $(CRR)_rC(O)NR^{9a}R^{9a}$, $(CRR)_rC(O)NR^{9a}OR^{9d}$,
 $(CRR)_rSO_2NR^{9a}R^{9a}$, $(CRR)_rC(O)OR^{9d}$, a $(CRR)_r-C_{3-10}$
 carbocyclic residue substituted with 0-5 R^{9e} , and a
 $(CRR)_r-5-10$ membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 15 substituted with 0-3 R^{9e} ;

R^{9a} , at each occurrence, is independently selected from H,
 methyl, C_{2-6} alkyl substituted with 0-3 R^{9e} , C_{3-8}
 alkenyl substituted with 0-3 R^{9e} , C_{3-8} alkynyl
 20 substituted with 0-3 R^{9e} , $(CH_2)_rC_{3-6}$ cycloalkyl, a
 $(CH_2)_r-C_{3-10}$ carbocyclic residue substituted with 0-5
 R^{9e} , and a $(CH_2)_r-5-10$ membered heterocyclic system
 containing 1-4 heteroatoms selected from N, O, and
 S, substituted with 0-3 R^{9e} ;

25 R^{9b} , at each occurrence, is independently selected from
 C_{1-6} alkyl substituted with 0-3 R^{9e} , C_{2-8} alkenyl
 substituted with 0-3 R^{9e} , C_{2-8} alkynyl substituted
 with 0-3 R^{9e} , a $(CH_2)_r-C_{3-6}$ carbocyclic residue
 30 substituted with 0-2 R^{9e} , and a $(CH_2)_r-5-6$ membered

heterocyclic system containing 1-4 heteroatoms
selected from N, O, and S, substituted with 0-3 R^{9e};

R^{9d}, at each occurrence, is independently selected from H,
5 methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{9e},
C₃₋₆ alkenyl substituted with 0-3 R^{9e}, C₃₋₆ alkynyl
substituted with 0-3 R^{9e}, a C₃₋₁₀ carbocyclic residue
substituted with 0-3 R^{9e}, and a (CH₂)_{r-5-6} membered
heterocyclic system containing 1-4 heteroatoms
10 selected from N, O, and S, substituted with 0-3 R^{9e};

R^{9e}, at each occurrence, is independently selected from
C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆
cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃,
15 (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅
alkyl, (CH₂)_rNR^{9f}R^{9f}, and (CH₂)_rphenyl;

R^{9f}, at each occurrence, is independently selected from H,
C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

20 R¹⁰ is selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
alkynyl, (CRR)_rOH, (CRR)_rSH, (CRR)_rOR^{10d},
(CRR)_rS(O)_pR^{10d}, (CRR)_rC(O)R^{10b}, (CRR)_rNR^{10a}R^{10a},
(CRR)_rC(O)NR^{10a}R^{10a}, (CRR)_rC(O)NR^{10a}OR^{10d},
25 (CRR)_rSO₂NR^{10a}R^{10a}, (CRR)_rC(O)OR^{10d}, a (CRR)_r-C₃₋₁₀
carbocyclic residue substituted with 0-5 R^{10e}, and a
(CRR)_{r-5-10} membered heterocyclic system containing
1-4 heteroatoms selected from N, O, and S,
substituted with 0-3 R^{10e};

30

alternatively, R¹⁰ and R¹¹ join to form a C₃₋₆ cycloalkyl substituted with 0-2 R^{10g}, a 5-6 membered ring lactam substituted with 0-2 R^{10g}, or a 5-6 membered ring lactone substituted with 0-2 R^{10g};

5

R^{10a}, at each occurrence, is independently selected from H, methyl, C₂₋₆ alkyl substituted with 0-3 R^{10e}, C₃₋₈ alkenyl substituted with 0-3 R^{10e}, C₃₋₈ alkynyl substituted with 0-3 R^{10e}, (CH₂)_rC₃₋₆ cycloalkyl, a (CH₂)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{10e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{10e};

15 R^{10b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-3 R^{10e}, C₂₋₈ alkenyl substituted with 0-3 R^{10e}, C₂₋₈ alkynyl substituted with 0-3 R^{10e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{10e}, and a (CH₂)_r-5-6 membered
20 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{10e};

R^{10d}, at each occurrence, is independently selected from H, methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3 R^{10e}, C₃₋₆ alkenyl substituted with 0-3 R^{10e}, C₃₋₆ alkynyl substituted with 0-3 R^{10e}, a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{10e}, and a (CH₂)_r-5-6 membered heterocyclic system containing
25 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{10e};
30

- R^{10e} , at each occurrence, is independently selected from
 C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-6}
 cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$,
 5 $(CH_2)_rOC_{1-5}$ alkyl, OH, $-O-C_{1-6}$ alkyl, SH, $(CH_2)_rSC_{1-5}$
 alkyl, $(CH_2)_rNR^{10f}R^{10f}$, and $(CH_2)_rphenyl$;
- R^{10f} , at each occurrence, is independently selected from
 H, C_{1-6} alkyl, and C_{3-6} cycloalkyl;
- 10 R^{10g} is selected from $(CHR)_qOH$, $(CHR)_qSH$, $(CHR)_qOR^{10d}$,
 $(CHR)_qS(O)_pR^{10d}$, $(CHR)_rC(O)R^{10b}$, $(CHR)_qNR^{10a}R^{10a}$,
 $(CHR)_rC(O)NR^{10a}R^{10a}$, $(CHR)_rC(O)NR^{10a}OR^{10d}$,
 $(CHR)_qSO_2NR^{10a}R^{10a}$, $(CHR)_rC(O)OR^{10d}$, and a $(CHR)_r-C_{3-10}$
 15 carbocyclic residue substituted with 0-5 R^{10e} ;
- R^{11} , is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}
 alkynyl, $(CRR)_rOH$, $(CRR)_rSH$, $(CRR)_rOR^{11d}$,
 $(CRR)_rS(O)_pR^{11d}$, $(CRR)_rC(O)R^{11b}$, $(CRR)_rNR^{11a}R^{11a}$,
 20 $(CRR)_rC(O)NR^{11a}R^{11a}$, $(CRR)_rC(O)NR^{11a}OR^{11d}$,
 $(CRR)_rSO_2NR^{11a}R^{11a}$, $(CRR)_rC(O)OR^{11d}$, a $(CRR)_r-C_{3-10}$
 carbocyclic residue substituted with 0-5 R^{11e} , and a
 $(CRR)_r-5-10$ membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S,
 25 substituted with 0-3 R^{11e} ;
- R^{11a} , at each occurrence, is independently selected from
 H, methyl, C_{2-6} alkyl substituted with 0-3 R^{11e} , C_{3-8}
 alkenyl substituted with 0-3 R^{11e} , C_{3-8} alkynyl
 30 substituted with 0-3 R^{11e} , $(CH_2)_rC_{3-6}$ cycloalkyl, a
 $(CH_2)_r-C_{3-10}$ carbocyclic residue substituted with 0-5

R^{11e}, and a (CH₂)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{11e};

5 R^{11b}, at each occurrence, is independently selected from C₁₋₆ alkyl substituted with 0-3 R^{11e}; C₂₋₈ alkenyl substituted with 0-3 R^{11e}, C₂₋₈ alkynyl substituted with 0-3 R^{11e}, a (CH₂)_r-C₃₋₆ carbocyclic residue substituted with 0-2 R^{11e}, and a (CH₂)_r-5-6 membered
10 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{11e};

R^{11d}, at each occurrence, is independently selected from H, methyl, -CF₃, C₂₋₆ alkyl substituted with 0-3
15 R^{11e}, C₃₋₆ alkenyl substituted with 0-3 R^{11e}, C₃₋₆ alkynyl substituted with 0-3 R^{11e}, a C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{11e}, and a (CH₂)_r-5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S,
20 substituted with 0-3 R^{11e};

R^{11e}, at each occurrence, is independently selected from C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₆ cycloalkyl, Cl, F, Br, I, CN, NO₂, (CF₂)_rCF₃,
25 (CH₂)_rOC₁₋₅ alkyl, OH, -O-C₁₋₆ alkyl, SH, (CH₂)_rSC₁₋₅ alkyl, (CH₂)_rNR^{11f}R^{11f}, and (CH₂)_rphenyl;

R^{11f}, at each occurrence, is independently selected from H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

30

- R^{12} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CRR)_qOH$, $(CRR)_qSH$, $(CRR)_qOR^{12d}$, $(CRR)_qS(O)_pR^{12d}$, $(CRR)_rC(O)R^{12b}$, $(CRR)_rNR^{12a}R^{12a}$, $(CRR)_rC(O)NR^{12a}R^{12a}$, $(CRR)_rC(O)NR^{12a}OR^{12d}$,
 5 $(CRR)_qSO_2NR^{12a}R^{12a}$, $(CRR)_rC(O)OR^{12d}$, a $(CRR)_r-C_{3-10}$ carbocyclic residue substituted with 0-5 R^{12e} , and a $(CRR)_r-5-10$ membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{12e} ;
 10 R^{12a} , at each occurrence, is independently selected from H, methyl, C_{2-6} alkyl substituted with 0-3 R^{12e} , C_{3-8} alkenyl substituted with 0-3 R^{12e} , C_{3-8} alkynyl substituted with 0-3 R^{12e} , $(CH_2)_rC_{3-6}$ cycloalkyl, a
 15 $(CH_2)_r-C_{3-10}$ carbocyclic residue substituted with 0-5 R^{12e} , and a $(CH_2)_r-5-10$ membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{12e} ;
 20 R^{12b} , at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-3 R^{12e} , C_{2-8} alkenyl substituted with 0-3 R^{12e} , C_{2-8} alkynyl substituted with 0-3 R^{12e} , a $(CH_2)_r-C_{3-6}$ carbocyclic residue substituted with 0-2 R^{12e} , and a $(CH_2)_r-5-6$ membered
 25 heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{12e} ;
 R^{12d} , at each occurrence, is independently selected from H, methyl, $-CF_3$, C_{2-6} alkyl substituted with 0-3
 30 R^{12e} , C_{3-6} alkenyl substituted with 0-3 R^{12e} , C_{3-6} alkynyl substituted with 0-3 R^{12e} , a C_{3-10}

carbocyclic residue substituted with 0-3 R^{12e} , and a $(CH_2)_r$ -5-6 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{12e} ;

5

R^{12e} , at each occurrence, is independently selected from C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-6} cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, $-O-C_{1-6}$ alkyl, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{12f}R^{12f}$, and $(CH_2)_r$ phenyl;

10

R^{12f} , at each occurrence, is selected from H, C_{1-6} alkyl, and C_{3-6} cycloalkyl;

15 R^{13} , at each occurrence, is independently selected from H, and C_{1-4} alkyl substituted with 0-1 R^{13b} , -OH, $-NH_2$, F, Cl, Br, I, $-OR^{13a}$, $-N(R^{13a})_2$, and C_{1-4} alkyl substituted with 0-3 R^{13b} ;

20 R^{13b} , at each occurrence, is independently selected from -OH, -SH, $-NR^{13c}R^{13c}$, $-C(O)NR^{13c}R^{13c}$, and $-NHC(O)R^{13c}$;

R^{13c} is selected from H, C_{1-4} alkyl and C_{3-6} cycloalkyl;

25 R^{14} is independently selected from H, and C_{1-4} alkyl substituted with 0-1 R^{14b} ;

R^{14b} , at each occurrence, is independently selected from -OH, -SH, $-NR^{14c}R^{14c}$, $-C(O)NR^{14c}R^{14c}$, and $-NHC(O)R^{14c}$;

30

R^{14c} is selected from H, C_{1-4} alkyl and C_{3-6} cycloalkyl;

R¹⁶ is selected from H, C₁₋₄ alkyl substituted with 0-3 R^{16a}, and C₃₋₆ cycloalkyl substituted with 0-3 R^{16a};

R^{16a} is selected from C₁₋₄ alkyl, -OH, -SH, -NR^{16c}R^{16c},
5 -C(O)NR^{16c}R^{16c}, and -NHC(O)R^{16c};

R^{16c} is selected from H, C₁₋₄ alkyl and C₃₋₆ cycloalkyl;

R¹⁷ is selected from H, C₁₋₄ alkyl, and C₃₋₄ cycloalkyl;

10

R¹⁸ is selected from H, C₁₋₄ alkyl, and C₃₋₄ cycloalkyl;

R¹⁹ is selected from H, C₁₋₄ alkyl, C₃₋₄ cycloalkyl,
-C(O)H, and -C(O)-C₁₋₄alkyl;

15

R²⁴, at each occurrence, is independently selected from H
and C₁₋₄alkyl;

alternatively, two R²⁴s, along with the carbon atom to
20 which they are attached, join to form a C₃₋₆
carbocyclic ring;

R²⁵, at each occurrence, is independently selected from H,
C₁₋₄alkyl, OH, NH₂, -O-C₁₋₄ alkyl, NR^{25a}R^{25a},
25 C(O)NR^{25a}R^{25a}, NR^{25a}C(O)R^{25b}, NR^{25a}C(O)OR^{25d},
OC(O)NR^{25a}R^{25a}, and (CHR)_rC(O)OR^{25d};

alternatively, two R²⁵s, along with the carbon atom or
atoms to which they are attached, join to form a C₃₋₆
30 carbocyclic ring;

R^{25a}, at each occurrence, is independently selected from H,
and C₁₋₄ alkyl,

5 R^{25b}, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

R^{25d}, at each occurrence, is independently selected from
C₁₋₄ alkyl, C₃₋₆ alkenyl, and C₃₋₆ alkynyl;

10 R²⁶ is selected from C₁₋₄ alkyl;

n is selected from 0, 1, 2, and 3;

l is selected from 0 and 1;

15

m is selected from 0 and 1;

p, at each occurrence, is selected from 0, 1, or 2;

20 q, at each occurrence, is selected from 1, 2, 3, or 4;

r, at each occurrence, is selected from 0, 1, 2, 3, or 4;

s is selected from 0 and 1; and

25

t is selected from 1, 2 and 3.

2. The compound of claim 1, wherein:

30 R¹⁶ is selected from H, C₁₋₄ alkyl substituted with 0-1

R^{16a}, wherein the alkyl is selected from methyl,
ethyl, propyl, i-propyl, butyl, i-butyl, and
s-butyl, and C₃₋₄ cycloalkyl substituted with 0-3

35 R^{16a} wherein the cycloalkyl is selected from
cyclopropyl and cyclobutyl;

R^{16a} is selected from methyl, ethyl, propyl, i-propyl, -OH, -SH, -NR^{16c}R^{16c}, -C(O)NR^{16c}R^{16c}, and -NHC(O)R^{16c};

5 R^{16c} is selected from H, methyl, ethyl, propyl, i-propyl, butyl, cyclopropyl, cyclopentyl, and cyclohexyl; and

R¹⁷ is selected from H, methyl, ethyl, propyl, and i-propyl.

10

3. The compound of claims 1-2, wherein:

R⁹ and R¹¹ are H; and

15 R⁸ and R¹⁰ are independently selected from H, methyl, ethyl, propyl, i-propyl, butyl, and cyclopropyl.

4. The compound of claims 1-3, wherein:

20 R³ is selected from (CRR)_qOH, (CRR)_qSH, (CRR)_qOR^{3d}, (CRR)_qS(O)_pR^{3d}, (CRR)_rC(O)R^{3b}, (CRR)_qNR^{3a}R^{3a}, (CRR)_rC(O)NR^{3a}R^{3a}, (CRR)_rC(O)NR^{3a}OR^{3d}, (CRR)_qSO₂NR^{3a}R^{3a}, (CRR)_rC(O)OR^{3d}, a (CRR)_r-C₃₋₁₀ carbocyclic residue substituted with 0-5 R^{3e}, and a
25 (CRR)_r-5-10 membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3e} wherein the heterocyclic system is selected from pyridinyl, thiophenyl, furanyl, indazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl,
30 benzisoxazolyl, quinolinyl, isoquinolinyl, imidazolyl, indolyl, indolinyl, isoindolyl, isothiadiazolyl, isoxazolyl, piperidinyl, pyrrazolyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, 1,2,4-triazolyl, 1,2,3-

35

triazolyl, tetrazolyl, thiadiazolyl, thiazolyl,
oxazolyl, pyrazinyl, and pyrimidinyl;

R⁶ is selected from H, (CRR)_qOH, (CRR)_qSH, (CRR)_qOR^{6d},
 5 (CRR)_qS(O)_pR^{6d}, (CRR)_rC(O)R^{6b}, (CRR)_qNR^{6a}R^{6a},
 (CRR)_rC(O)NR^{6a}R^{6a}, (CRR)_rC(O)NR^{6a}OR^{6d},
 (CRR)_qSO₂NR^{6a}R^{6a}, (CRR)_rC(O)OR^{6d}, a (CRR)_r-C₆₋₁₀
 carbocyclic residue substituted with 0-5 R^{6e}, and a
 (CRR)_r-5-10 membered heterocyclic system containing
 10 1-4 heteroatoms selected from N, O, and S,
 substituted with 0-6 R^{6e} wherein the heterocyclic
 system is selected from pyridinyl, thiophenyl,
 furanyl, indazolyl, benzothiazolyl, benzimidazolyl,
 benzothiophenyl, benzofuranyl, benzoxazolyl,
 15 benzisoxazolyl, quinolinyl, isoquinolinyl,
 imidazolyl, indolyl, indolinyl, isoindolyl,
 isothiadiazolyl, isoxazolyl, piperidinyl,
 pyrrazolyl, pyrrolidinyl, tetrahydrofuranyl,
 tetrahydrothiophenyl, 1,2,4-triazolyl, 1,2,6-
 20 triazolyl, tetrazolyl, thiadiazolyl, thiazolyl,
 oxazolyl, pyrazinyl, and pyrimidinyl;

R⁷ is H;

25 R¹² is selected from H, methyl, ethyl, and propyl;

alternatively, R³ and R¹² join to form a C₃₋₆ cycloalkyl
 substituted with 0-2 R^{3g}, a 5-6 membered lactam ring
 substituted with 0-2 R^{3g}, or a 5-6 membered lactone
 30 ring substituted with 0-2 R^{3g}; and

m + 1 is equal to 1.

5. The compound of claims 1-4, wherein:

35

R¹ is selected from phenyl substituted with 0-3 R⁴ and a
 5-10 membered heteroaryl system substituted with 0-3
 R⁴, wherein the heteroaryl is selected from
 benzimidazolyl, benzofuranyl, benzothiofuranyl,
 5 benzoxazolyl, benzthiazolyl, benztriazolyl,
 benztetrazolyl, benzisoxazolyl, benzisothiazolyl,
 benzimidazalonyl, cinnolinyl, furanyl, imidazolyl,
 indazolyl, indolyl, isoquinolinyl isothiazolyl,
 isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl,
 10 pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl,
 quinazolinyl, quinolinyl, thiazolyl, thienyl, and
 tetrazolyl;

R² is selected from phenyl substituted with 0-3 R⁵ and a
 15 5-10 membered heteroaryl system containing 1-4
 heteroatoms substituted with 0-3 R⁵, wherein the
 heteroaryl system is selected from benzimidazolyl,
 benzofuranyl, benzothiofuranyl, benzoxazolyl,
 benzthiazolyl, benztriazolyl, benztetrazolyl,
 20 benzisoxazolyl, benzisothiazolyl, benzimidazalonyl,
 cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl,
 isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl,
 pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl,
 pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl,
 25 thiazolyl, thienyl, and tetrazolyl.

6. The compound of claims 1-5, wherein:

30 X is CHR¹⁶R¹⁷;

R⁴, at each occurrence, is selected from C₁₋₈ alkyl, C₂₋₈
 alkenyl, C₂₋₈ alkynyl, (CR'R')_rC₃₋₆ cycloalkyl, Cl,
 Br, I, F, NO₂, CN, (CR'R')_rNR^{4a}R^{4a}, (CR'R')_rOH,
 (CR'R')_rOR^{4d}, (CR'R')_rSH, (CR'R')_rSR^{4d},

$(CR'R')_rC(O)OH$, $(CR'R')_rC(O)R^{4b}$, $(CR'R')_rC(O)NR^{4a}R^{4a}$,
 $(CR'R')_rNR^{4f}C(O)R^{4b}$, $(CR'R')_rC(O)OR^{4d}$,
 $(CR'R')_rOC(O)R^{4b}$, $(CR'R')_rNR^{4f}C(O)OR^{4d}$,
 $(CR'R')_rOC(O)NR^{4a}R^{4a}$, $(CR'R')_rNR^{4a}C(O)NR^{4a}R^{4a}$,
5 $(CR'R')_rS(O)_pR^{4b}$, $(CR'R')_rS(O)_2NR^{4a}R^{4a}$,
 $(CR'R')_rNR^{4f}S(O)_2R^{4b}$, $(CR'R')_rNR^{4f}S(O)_2NR^{4a}R^{4a}$, C_{1-6}
haloalkyl, and $(CR'R')_r$ phenyl substituted with 0-3
 R^{4e} ;

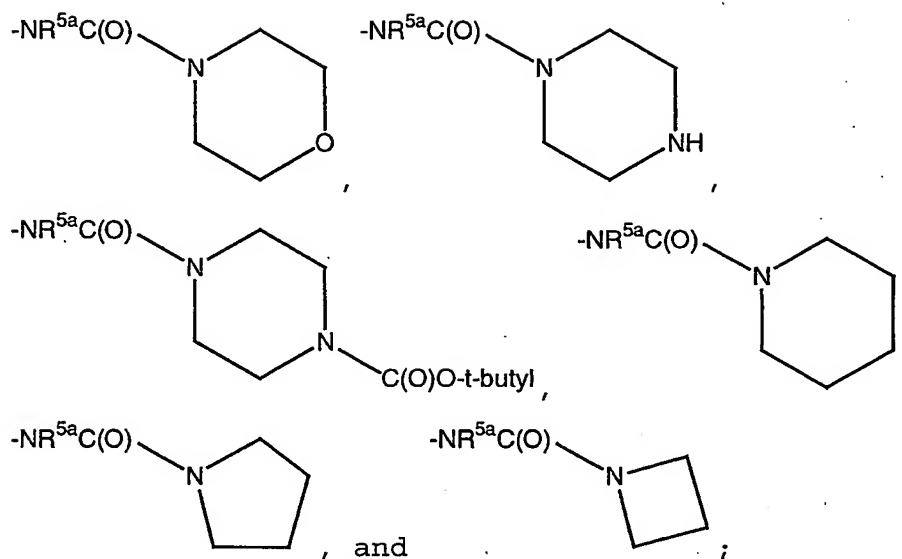
10 alternatively, two R^4 on adjacent atoms join to form
 $-O-(CH_2)-O-$;

R^{4a} , at each occurrence, is independently selected from H,
methyl, ethyl, propyl, i-propyl, butyl, s-butyl,
15 i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl,
and a $(CH_2)_r-C_{3-6}$ carbocyclic residue selected from
cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

R^{4b} , at each occurrence, is selected from methyl, ethyl,
20 propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl,
pentyl, hexyl, allyl, propargyl, a $(CH_2)_r-C_{3-6}$
carbocyclic residue substituted with 0-3 R^{4e} , wherein
the carbocyclic residue is selected from
cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl,
25 and a $(CH_2)_r-5-6$ membered heterocyclic system
containing 1-4 heteroatoms selected from N, O, and
S, substituted with 0-2 R^{4e} , wherein the heterocyclic
system is selected from pyridinyl, thiophenyl,
furanyl, indazolyl, benzothiazolyl, benzimidazolyl,
30 benzothiophenyl, benzofuranyl, benzoxazolyl,
benzisoxazolyl, quinolinyl, isoquinolinyl,
imidazolyl, indolyl, indolinyl, isoindolyl,
isothiadiazolyl, isoxazolyl, piperidinyl,
pyrrolazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl,

tetrazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazinyl, and pyrimidinyl;

- 5 R^{4d} , at each occurrence, is selected from H, methyl, CF_3 , ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a $(CH_2)_rC_{3-6}$ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
- 10 R^{4e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{4f}R^{4f}$, and $(CH_2)_rphenyl$;
- 15 R^{4f} , at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, and cyclopropyl, cyclobutyl, and phenyl;
- 20 R^5 , at each occurrence, is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl, $(CR'R')_rC_{3-6}$ cycloalkyl, Cl, Br, I, F, NO_2 , CN, $(CR'R')_rNR^{5a}R^{5a}$, $(CR'R')_rOH$, $(CR'R')_rOR^{5d}$, $(CR'R')_rSH$, $(CR'R')_rC(O)H$, $(CR'R')_rSR^{5d}$, $(CR'R')_rC(O)OH$, $(CR'R')_rC(O)R^{5b}$, $(CR'R')_rC(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{5f}C(O)R^{5b}$, $(CR'R')_rC(O)OR^{5d}$, $(CR'R')_rOC(O)R^{5b}$, $(CR'R')_rNR^{5f}C(O)OR^{5d}$, $(CR'R')_rOC(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{5a}C(O)NR^{5a}R^{5a}$, $(CR'R')_rNR^{7a}C(O)NR^{7a}R^{7a}$, $(CR'R')_rNR^{7a}C(O)O(CR'R')_rR^{7d}$, $(CR'R')_rS(O)_pR^{5b}$, $(CR'R')_rS(O)_2NR^{5a}R^{5a}$, $(CR'R')_rNR^{5f}S(O)_2R^{5b}$, C_{1-6} haloalkyl, and $(CHR')_rphenyl$ substituted with 0-3 R^{5e} , a $(CRR)_{r-5-10}$ membered heterocyclic system containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-2 R^{5c} ,
- 25
- 30



5 alternatively, two R^5 on adjacent atoms join to form
 $-O-(CH_2)-O-$;

R^{5a} , at each occurrence, is independently selected from H,
 methyl, ethyl, propyl, i-propyl, butyl, s-butyl,
 10 i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl,
 and a $(CH_2)_r-C_{3-10}$ carbocyclic residue substituted
 with 0-1 R^{5e} , wherein the carbocyclic residue is
 selected from cyclopropyl, cyclobutyl, cyclopentyl,
 cyclohexyl, phenyl and naphthyl;

15 R^{5b} , at each occurrence, is selected from methyl, ethyl,
 propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl,
 pentyl, hexyl, allyl, propargyl, a $(CH_2)_r-C_{3-6}$
 carbocyclic residue selected from cyclopropyl,
 20 cyclobutyl, cyclopentyl, cyclohexyl, and phenyl; and
 a $(CH_2)_r-5-6$ membered heterocyclic system containing
 1-4 heteroatoms selected from N, O, and S, wherein
 the heterocyclic system is selected from pyridinyl,
 thiophenyl, furanyl, indazolyl, azetidyl,
 25 benzothiazolyl, benzimidazolyl, benzothiophenyl,
 benzofuranyl, benzoxazolyl, benzisoxazolyl,
 quinolinyl, isoquinolinyl, imidazolyl, indolyl,

indoliny, isoindolyl, isothiadiazo, isoxazoly, morpholinyl, piperidinyl, pyrroly, 2,5-dihydropyrroly, pyrrazoly, 1,2,4-triazoly, 1,2,3-triazoly, tetrazoly, thiadiazo, thiazoly, oxazoly, pyrazinyl, and pyrimidinyl;

R^{5d} , at each occurrence, is selected from H, methyl, CF_3 , ethyl, propyl, i-propyl, butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl, allyl, propargyl, and a $(CH_2)_r-C_{3-6}$ carbocyclic residue selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

R^{5e} , at each occurrence, is selected from C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, Cl, F, Br, I, CN, NO_2 , $(CF_2)_rCF_3$, $(CH_2)_rOC_{1-5}$ alkyl, OH, SH, $(CH_2)_rSC_{1-5}$ alkyl, $(CH_2)_rNR^{4f}R^{4f}$, and $(CH_2)_rphenyl$; and

R^{5f} , at each occurrence, is selected from H, methyl, ethyl, propyl, i-propyl, butyl, and cyclopropyl, cyclobutyl, and phenyl.

7. The compound of claims 1-6, wherein:

R^5 is selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, pentyl, hexyl, CF_3 , CF_2CF_3 , CF_2H , OCF_3 , Cl, Br, I, F, SCF_3 , $NR^{5a}R^{5a}$, $NHC(O)OR^{5a}$, $NHC(O)R^{5b}$, and $NHC(O)NHR^{5a}$; and

R^{12} is selected from H and methyl.

8. A compound of claims 1-7, wherein:

Z is $-NC(O)-$, $-NHC(S)-$, $-NHC(O)NH-$, $-NHC(S)NH-$, $-NHOSO_2-$, $-NR^{19}-CH_2-$;

X is $-\text{CHR}^{16}\text{NR}^{17}-$;

R¹ is selected from phenyl substituted with 0-3 R⁴, and a
5 5-10 membered heteroaryl system substituted with 0-2
R⁴, wherein the heteroaryl is selected from indolyl,
and pyridyl;

R² is phenyl substituted with 0-2 R⁵;

10 R³ is selected from $(\text{CRR})_q\text{OH}$, $(\text{CRR})_q\text{OR}^{3d}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{OH}$,
 $(\text{CH}_2)_r\text{C}(\text{O})\text{NR}^{3a}\text{R}^{3a}$, $(\text{CHR})_r\text{C}(\text{O})\text{NR}^{3a}\text{OR}^{3d}$, $(\text{CH}_2)\text{C}(\text{O})\text{R}^{3b}$,
 $(\text{CH}_2)_r\text{C}(\text{O})\text{OR}^{3d}$, and (CH_2) -phenyl;

15 R^{3a} is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, s-butyl, t-butyl, allyl, CH_2CF_3 ,
 $\text{C}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, cyclopropyl, 1-methylcyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and
benzyl;

20 R^{3b} is selected from pyrrolidinyl, pyrrolid-3-enyl, and
morpholinyl;

R^{3d} is selected from methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, t-butyl and benzyl;

25 R is selected from H, methyl, ethyl, propyl, i-propyl,
butyl, i-butyl, s-butyl, pentyl, neopentyl, phenyl
and benzyl;

30 R⁴ is selected from methyl, ethyl, propyl, i-propyl,
butyl, ethylene, OCH_3 , OCF_3 , SCH_3 , SO_2CH_3 , Cl, F, Br,
CN;

alternatively, two R⁴ join to form $-\text{O}-(\text{CH}_2)-\text{O}-$;

35

R⁶ is selected from H, methyl, ethyl, propyl, i-propyl, butyl, C(O)OCH₃, C(O)NHCH₂CH₃;

R⁷ is H;

5

R¹⁶ is selected from H and methyl;

R¹⁷ is selected from H and methyl;

10 m is 0 ;

l is 0

r is 0 or 1; and

15

q is 1.

9. The compound of claim 1, wherein the compound is selected from:

20

N-[(3S)-1-[(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-yl]-3-trifluoromethyl-benzamide;

25

1-[(3S)-1-[(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-yl]-3-(3-trifluoromethylphenyl)-urea;

30

{2-[(3S)-1-[(1S, 2S)-1-[(2,4-Dimethyl-benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-pyrrolidin-3-ylcarbonyl]-4-trifluoromethyl-phenyl}-carbamic acid tert-butyl ester;

2-Amino-N-[(3S)-1-[(1S, 2S)-1-[(2,4-dimethyl-
benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-
pyrrolidin-3-yl]-5-trifluoromethyl-benzamide;

5 3-Amino-N-[(3S)-1-[(1S, 2S)-1-[(2,4-dimethyl-
benzylamino)-methyl]-2-hydroxy-pentyl]-2-oxo-
pyrrolidin-3-yl]-5-trifluoromethyl-benzamide; and

2-Amino-N-{(3S)-1-[(1S)-1-tert-butylcarbonyl-2-(2,4-
10 dimethyl-benzylamino)-ethyl]-2-oxo-pyrrolidin-3-yl}-
5-trifluoromethyl-benzamide.

10. A pharmaceutical composition, comprising a
pharmaceutically acceptable carrier and a therapeutically
15 effective amount of a compound of claims 1-9.

11. A method for modulation of chemokine or
chemokine receptor activity comprising administering to a
patient in need thereof a therapeutically effective
20 amount of a compound of claims 1-9.

12. A method for modulation of MCP-1, MCP-2, MCP-3
and MCP-4, and MCP-5 activity that is mediated by the
CCR2 receptor comprising administering to a patient in
25 need thereof a therapeutically effective amount of a
compound of claims 1-9.

13. A method for modulation of MCP-1 activity
comprising administering to a patient in need thereof a
30 therapeutically effective amount of a compound of claims
1-9.

14. A method for treating disorders, comprising
administering to a patient in need thereof a
35 therapeutically effective amount of a compound of claims
1-9, said disorders being selected from osteoarthritis,

aneurism, fever, cardiovascular effects, Crohn's disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerularnephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

15. The method for treating disorders, of claim 14, wherein said disorders being selected from psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerularnephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

16. The method for treating disorders, of claim 15, wherein said disorders being selected from alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerularnephritis, asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

17. The method for treating disorders, of claim 16, wherein said disorders being selected from asthma, multiple sclerosis, arteriosclerosis, rheumatoid arthritis, restinosis, organ transplantation, and cancer.

18. A method for treating rheumatoid arthritis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claims 1-9.

5

19. A method for treating multiple sclerosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claims 1-9.

10

20. A method for treating atherosclerosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claims 1-9.

15

21. A method for treating asthma, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claims 1-9.

20

22. The method for treating disorders of claim 17, wherein said disorders being selected from restinosis, organ transplantation, and cancer.

25

23. A method for treating restinosis, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claims 1-9.

30

24. A method for treating organ transplantation, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claims 1-18.

25. A method for treating inflammatory diseases,
comprising administering to a patient in need thereof a
therapeutically effective amount of a compound of claims
5 1-9.

26. A method for modulation of CCR2 activity
comprising administering to a patient in need thereof a
therapeutically effective amount of a compound of claims
10 1-9.

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GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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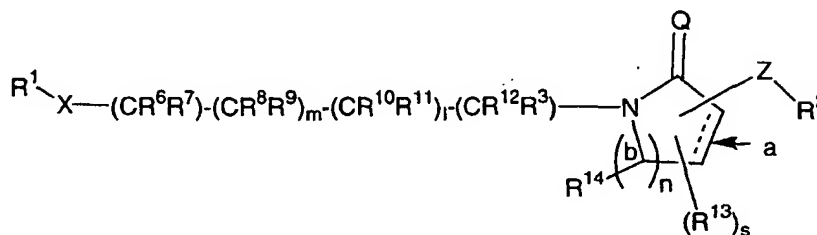
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[Continued on next page]

WO 2004/071449 A3

(54) Title: LACTAMS AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(57) Abstract: The present application describes modulators of MCP-1 of formula (I): or pharmaceutically acceptable salt forms thereof, useful for the prevention of asthma, multiple sclerosis, atherosclerosis, and rheumatoid arthritis.



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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(88) Date of publication of the international search report:
6 January 2005

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/04151

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C07D 207/273 US CL : 548/550 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 548/550 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CREGGE ET AL., Inhibition of Human Neutrophil Elastase. 4. Design, Synthesis, X-ray Crystallographic Analysis, and Structure-Activity Relationships for a Series of P2-Modified, Orally Active Peptidyl Pentafluoroethyl Ketones, Journal of Medicinal Chemistry, 1998, Volume 41, pages 2461-2480, especially page 2462	9
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search		Date of mailing of the international search report
17 August 2004 (17.08.2004)		
Name and mailing address of the ISA/US		Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230		Rebecca L Anderson Telephone No. (703)308-1235

INTERNATIONAL SEARCH REPORT

International appl. no.
 PCT/US04/04151

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
 because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1 and 2
 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
 Please See Continuation Sheet
3. ☒ Claims Nos.: 3-8 and 10-26
 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
 ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/04151

Continuation of Box II Reason 2:

The numerous variables , e.g. R1, X, R6, R7, R8, R9, m, R10, R11, R12, R3, b, n, R14, s, R13, a, Z, R2, Q, etc., and their voluminous, complex meanings and their virtual incomprehensible permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concisedescription for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same. The search will be performed on the first discernable invention which is the first compound of claim 9.

Continuation of B. FIELDS SEARCHED Item 3:

CAS ONLINE

STN structure search

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